NETHMAP 2009



Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands

rivm

SWAB

Download from SWAB.nl | 2026-11-12 14:20

NETHMAP
2009

Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands

rivm

SWAB

Download from SWAB.nl | 2026-11-12 14:20

Colophon

This report is published under the acronym NethMap by the SWAB, the Dutch Foundation of the Working Party on Antibiotic Policy, in collaboration with the RIVM, the National Institute for Public Health and the Environment of the Netherlands. SWAB is fully supported by a structural grant from the Ministry of Health, Welfare and Sports of the Netherlands. The information presented in NethMap is based on data from ongoing surveillance systems on the use of antimicrobial agents in human medicine and on the prevalence of resistance to relevant antimicrobial agents among medically important bacteria and viruses isolated from healthy individuals and patients in the community and from hospitalized patients. The document was produced on behalf of the SWAB by the Studio of the RIVM.
NethMap can be ordered from the SWAB secretariat, c/o Academic Medical Centre, Afdeling Infectieziekten, Tropische Geneeskunde en AIDS, F4-217, Postbus 22660, 1100 DD AMSTERDAM, The Netherlands, Tel. +31 20 566 60 99, Fax +31 20 697 22 86. NethMap is available from the website of the SWAB: www.swab.nl. The suggested citation is: "SWAB. NethMap 2009 – Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands."

Editors:
Prof Dr JE Degener, UMC Groningen
Dr Ir MN Mulders, RIVM Bilthoven

Persons actively involved in writing this report:
Dr PGM Filius, Erasmus MC Rotterdam
Drs AD Lindemans, Erasmus MC Rotterdam
Prof Dr JAA Hoogkamp-Korstanje, UMC Maastricht

Board-members of SWAB
Prof Dr JE Degener (chairman)
Prof Dr JM Prins (secretary)
Prof Dr BJ Kullberg (treasurer)
Prof Dr MJM Bonten
Prof Dr H Grundmann
Dr IC Gyssens
Dr NG Hartwig
Dr YG van der Meer
Prof Dr DJ Mevius
Dr JW Mouton
Dr S Natsch
Dr EE Stobberingh
Dr JWPM Overdiek
Prof Dr HA Verbrugh
Prof Dr ThJM Verheij

Members of SWAB's working group on surveillance of antimicrobial resistance
Prof Dr JAA Hoogkamp-Korstanje (chair)
Prof Dr JE Degener
Prof Dr H Grundmann
Dr R Hendrix
Dr M Leverstein - van Hall
Prof Dr DJ Mevius
Dr J Mouton
Dr Ir MN Mulders
Dr AJ de Neeling
Dr MAB van der Sande
Dr EE Stobberingh
Prof Dr HA Verbrugh

Members of SWAB's working group on surveillance of antimicrobial use
Dr PMG Filius (convener)
Drs AD Lindemans (coördinator)
Drs AJ Freitag- de Koster
Dr MM Kuyvenhoven
Drs TBY Liem
Dr PD van der Linden
Dr S Natsch
Dr AJ de Neeling

Download from SWAB.nl | 2026-11-12 14:20

Tabel 1 Centres contributing to the surveillance of antimicrobial resistance.

			COM	I U P	ISIS	M e n	Gon
Groningen	Delfzijl	Delfzicht Hospital				0	
	Groningen	Academic Medical Centre				0	0
		Regional Laboratory for Public Health		0	0	0	0
		Municipal Health Service Groningen					0
	Stadskanaal	Refaja Hospital				0	
	Winschoten	St Lucas Hospital				0	
	t Zandt	General practice	0				
Friesland	Leeuwarden	Regional Laboratory for Public Health		0		0	0
		Municipal Health Service Fryslan					0
Drente	Assen	General practice	0				
		Municipal Health Service Drenthe					0
	Emmen	Scheper Hospital				0	
Overijssel	Deventer	Deventer Hospital					0
		Regional Laboratory for Public Health				0	
	Enschede	Regional Laboratory for Public Health		0		0	0
		Municipal Health Service Twente					0
	Hardenberg	Regional Laboratory for Public Health				0	
	Zwolle	Isala Clinics					0
		Hanze laboratory				0	
		Regional Laboratory for Public Health		0			
Gelderland	Apeldoorn	Medical Laboraties ZCA			0	0	
	Arnhem	Regional Laboratory for Public Health				0	0
		Alysis Centre					0
		Hulpverlening Gelderland Midden					0
	Barneveld	General practice	0				
	Dieren	General practice	0				
	Doetinchem	Slingeland Hospital				0	
	Ede	Gelderse Vallei Hospital				0	
	Harderwijk	St Jansdal Hospital				0	
	Heerde	General practice	0				
	Nijmegen	University Medical Centre St Radboud		0		0	0
		Regional Laboratory for Public Health CWZ				0	0
		Municipal Health Service Nijmegen					0
	Zelhem	General practice	0				
Utrecht	Amersfoort	Meander Medical Centre				0	0
		General practice	0				
	Bilthoven	National Institute for Public Health and the Environment					
	Nieuwegein	Sint Antonius Hospital		0		0	0
	Utrecht	Diakonessenhuis				0	
		General practice	0				
		Neth Institute for Health Services Research NIVEL	0				
		Mesos Medical centre				0	
		SALTRO					0
		University Medical Centre			0	0	0
		Municipal Health Service Utrecht					0
	Zeist	Diakonessenhuis				0	
Noord Holland	Alkmaar	General practice	0				
		Medical Centre Alkmaar				0	0
	Amsterdam	Academic Medical Centre				0	0
		Academic Hospital VU				0	0
		General practice	0				
		Onze Lieve Vrouwe Gasthuis		0		0	0
		Regional Laboratory for Public Health					0
		Slotervaart Hospital				0	
		St Lucas Andreas Hospital				0	
		Municipal Health Service Amsterdam					0
	Baarn	Medical Centre I				0	
	Haarlem	General practice	0				
		Regional Laboratory for Public Health		0			
	Hilversum	Central Bacteriological Laboratory			0	0	
	Hoorn	Westfries Gasthuis				0	
	Huizen	General practice	0				
	Zaandam	Zaans Medical Centre				0	0

Download from SWAB.nl | 2026-11-12 14:20

Table 1 Continued

			COM	IUP	ISIS	Men	Gon
Zuid Holland	Capelle a/d IJssel	IJsselland Hospital				0	
	Delft	SSDZ laboratories			0	0	0
	's-Gravenhage	Bronovo Hospital		0		0	
		General practice	0				
		Leyenburg Hospital				0	0
		Regional Laboratory for Public Health				0	
		Rode Kruis / Juliana Children's Hospital				0	
		Medical Centre Haaglanden				0	0
		Municipal Health Service Den Haag					0
	Dordrecht	Regional Laboratory for Public Health				0	0
	Gorkum	Regional Laboratory for Public Health				0	
	Gouda	Groene Hart Hospital				0	
	Leiden	Diakonessenhuis		0		0	
		KML Laboratory				0	
		University Medical Centre					0
	Leiderdorp	Rijnland Hospital				0	
	Rotterdam	General practice	0				
		Erasmus University Medical Centre				0	0
		Ikazia Hospital					0
		Maasstadziekenhuis		0		0	
		Sophia Children's Hospital				0	
		St Franciscus Gasthuis				0	
		Municipal Health Service Rotterdam					0
	Schiedam	Vlietland Hospital				0	
	Spijkenisse	Ruwaard vd Putten Hospital				0	0
	Voorhout	General practice	0				
	Woerden	Zuwe Hofpoort Hospital				0	
Noord Brabant	Bergen op Zoom	Lievensberg Hospital			0	0	
	Breda	Amphia Hospital			0		0
		Municipal Health Service West-Brabant					0
	Eindhoven	Municipal Health Service Eindhoven					0
	Helmond	Municipal Health Service Zuidoost Brabant					0
	's Hertogenbosch	Jeroen Bosch Medical Centre					0
		Regional Laboratory for Public Health				0	
	Ravenstein	General practice	0				
	Roosendaal	Franciscus Hospital			0	0	
	Rosmalen	General practice	0				
	Tilburg	Regional Laboratory for Public Health		0	0	0	0
		Municipal Health Service Hart voor Brabant					0
	Uden	General practice	0				
	Veldhoven	Laboratory for Medical Microbiology				0	0
Limburg	Geleen	Municipal Health Service	0				
	Heerlen	Regional Laboratory for Public Health				0	0
		Atrium Medical Centre				0	0
	Maastricht	General practice	0				
		Nursing home Vivre location KLevarie	0				
		Nursing home De Zeven Bronnen	0				
		Academic Medical Centre		0		0	0
		Municipal Health Service Zuid-Limburg					0
	Roermond	Laurentius Hospital				0	0
	Sittard	Maasland Hospital				0	
	Venlo	VieCuri Medical Centre		0		0	0
		Municipal Health Service Noord- en Midden Limburg					0
	Weert	St Jansgasthuis				0	0
Zeeland	Goes	Regional Laboratory for Public Health		0	0	0	0
		Municipal Health Service Zeeland					0
	Middelburg	General practice	0				
	Terneuzen	General practice	0				
		Regional Laboratory for Public Health			0	0	0

COM=Community, IUP=Intensive Cares/Urology Services/Pulmonology Services, ISIS=Infectious Diseases Information System, Men=Meningitis Surveillance, Gon=Gonorrhoea Surveillance.

Download from SWAB.nl | 2026-11-12 14:20

Centres contributing to the surveillance of the use of antimicrobial agents

Community usage

Foundation for Pharmaceutical Statistics SFK, The Hague.

Hospital usage

We hereby recognize the important contributions of hospital pharmacists of the following hospitals in collecting and providing quantitative data to SWAB on the use of antimicrobial agents in their respective institutions listed hereunder:

Alkmaar, Medisch Centrum Alkmaar; Almelo, Twenteborg Ziekenhuis; Amersfoort, Meander Medisch Centrum; Amstelveen, Ziekenhuis Amstelland; Amsterdam, Academisch Medisch Centrum; Amsterdam, VU Medisch Centrum; Amsterdam, BovenIJ Ziekenhuis; Amsterdam, O.L. Vrouwe Gasthuis; Amsterdam, Slotervaart Ziekenhuis; Apeldoorn, Gelre ziekenhuizen; Arnhem, Rijnstate Ziekenhuis; Assen, Wilhelmina Ziekenhuis; Bergen op Zoom, Ziekenhuis Lievensberg; Blaricum, Tergooi Ziekenhuizen; Boxmeer, Maasziekenhuis; Breda, Amphia Ziekenhuis; Capelle aan den IJssel, IJsselland Ziekenhuis; Coevorden/ Hardenberg, Streekziekenhuis; Delft, Reinier de Graaf Groep; Den Haag, Bronovo Ziekenhuis; Den Haag, Leyenburg Ziekenhuis; en Haag, RKZ/JKZ; Den Helder, Gemini Ziekenhuis; Deventer, St. Deventer Ziekenhuizen; Doetinchem, Slingeland Ziekenhuis; Dokkum, Streekziekenhuis; Dordrecht, Albert Schweitzer Ziekenhuis; Drachten, Ziekenhuis Nij Smellinghe; Ede, Ziekenhuis Gelderse Vallei; Eindhoven, Catharina Ziekenhuis; Eindhoven, Maxima Medisch Centrum; Enschede, Medisch Spectrum Twente; Geldrop, St. Anna Zorggroep; Goes, St. Oosterschelde Ziekenhuizen; Gorinchem, Rivas Zorggroep; Gouda, Groene Hart Ziekenhuis; Groningen, Groningen Universitair Medisch Centrum; Groningen, Delfzicht Ziekenhuis; Groningen, Martini Ziekenhuis; Groningen, Refaja Ziekenhuis; Haarlem, Kennemer Gasthuis; Haarlem, Spaarne Ziekenhuis; Harderwijk, Ziekenhuis St. Jansdal; Heerlen, Atrium Medisch Centrum; Hengelo, Ziekenhuisgroep Twente; ’s Hertogenbosch, Jeroen Bosch Ziekenhuis; Hilversum, Tergooiziekenhuis; Hoorn, Westfries Gasthuis; Leeuwarden, Medisch Centrum Leeuwarden; Leiden, Diakonessenhuis; Leiden, Leids Universitair Medisch Centrum; Leiderdorp, Rijnland Ziekenhuis; Leidschendam, Medisch Centrum Haaglanden; Maastricht, Academisch Ziekenhuis Maastricht; Nieuwegein St. Antonius Ziekenhuis; Nijmegen, Canisius Wilhelmina Ziekenhuis; Nijmegen, Universitair Medisch Centrum St. Radboud; Oss, Ziekenhuis Bernhoven; Purmerend, Waterlandziekenhuis; Roermond, Laurentius Ziekenhuis; Rotterdam, Erasmus MC; Rotterdam, Ikazia Ziekenhuis; Rotterdam, Maasstadziekenhuis (voorheen Medisch Centrum Rijnmond-Zuid); Rotterdam, Sint Franciscus Gasthuis; Sittard, Maaslandziekenhuis; Sneek, Antonius Ziekenhuis; Spijkenisse, Ruwaard van Putten Ziekenhuis; Terneuzen, ZorgSaam Zeeuws-Vlaanderen; Tiel, Ziekenhuis Rivierenland; Tilburg, Elisabeth Ziekenhuis; Tilburg, Tweesteden Ziekenhuis; Utrecht, Diakonessenhuis Utrecht; Utrecht, Mesos Medisch Centrum; Utrecht, Universitair Medisch Centrum Utrecht; Veghel, Ziekenhuis Bernhoven; Veldhoven, Maxima Medisch Centrum; Venlo, VieCuri Medisch Centrum voor Noord-Limburg; Venray, Stichting ZALV; Vlaardingen, Vlietland Ziekenhuis; Vlissingen, Ziekenhuis Walcheren; Weert, St. Jans Gasthuis; Winschoten, Sint Lucas Ziekenhuis; Woerden, Hofpoort Ziekenhuis; Zaandam, Zaans Medisch Centrum; Zeist, Diakonessenhuis Zeist; Zevenaar, Streekziekenhuis; Zoetermeer, ’t Lange Land Ziekenhuis; Zutphen, Het Spittaal; Zwolle, Isala Klinieken.

Acknowledgements

We thank mrs Y Beeuwkes for drawing the figures and secretarial assistance, drs J Muilwijk for collecting and analysing the ISIS data, and mrs KAM Haverkamp (Publishing Department RIVM) for preparing this report for printing.

Download from SWAB.nl | 2026-11-12 14:20

Preface

This is the seventh SWAB/RIVM NethMap report on the use of antibiotics and trends in antimicrobial resistance in the Netherlands in 2008 and before. NethMap is a product of cooperative efforts of members of The Netherlands Society for Infectious Diseases, The Netherlands Society of Hospital Pharmacists and the Netherlands Society for Medical Microbiology. In 1996, the three societies created the Dutch Working Group on Antibiotic Policy, known as SWAB (Stichting Werkgroep Antibiotica Beleid). SWAB's mission is to manage, limit and prevent the emergence of resistance to antimicrobial agents among medically important species of micro organisms in the Netherlands, thereby contributing to the quality of care in the Netherlands.

Because of the multidisciplinary composition of SWAB, this foundation can be considered the Dutch equivalent of the Intersectoral Coordinating Mechanisms (ICM's), recommended by the European Union (2001), to control emerging antimicrobial resistance and promote rational antibiotic use.

SWAB has started several major initiatives to achieve its goals. Among these are training programmes for the rational prescription of antimicrobial drugs, development of evidence-based prescription guidelines, the implementation of tailor-made hospital guides for antibiotic prophylaxis and therapy, and an integrated nationwide surveillance system for antibiotic use and antimicrobial resistance. These initiatives are corresponding well with the recommendations by the Dutch Council of Health Research (2001).

Following these recommendations SWAB's work was and still is made possible by structural funds provided by the Ministry of Health, Welfare and Sports and through the Centre for Infectious Disease Control Netherlands (Centrum Infectieziektebestrijding, CIb) at the National Institute for Public Health and the Environment (RIVM).

NethMap 2009 extends and updates the information of the annual reports since 2003. NethMap parallels the monitoring system of antimicrobial resistance and antibiotic usage in animals in the Netherlands, called MARAN, by the Veterinary Antibiotic Usage and Resistance Surveillance Working Group (VANTURES, see www.cvi.wur.nl). Recently, MARAN 2007 has been published. Together NethMap and MARAN are aiming at providing a comprehensive overview of antibiotic use in the Netherlands in man and in animal husbandry and therefore are offering insight into the ecological pressure which is associated with emerging resistance trends.

The interaction between the human and veterinarian areas of antibiotic use and resistance is explored in a working group started in 2003 by the Ministry of health, Welfare and Sports and that of Agriculture, Nature and Food Quality. Both SWAB and its veterinary sister group are represented in this interdepartmental working group in which the evolution of antibiotic use and resistance in the Netherlands is discussed on the basis of SWAB's and MARAN's surveillance data.

NethMap is thus providing extensive and detailed insight in the Dutch state of medically important antimicrobial resistance, and compares well with the data of the European Antimicrobial Resistance Surveillance System (EARSS, see www.rivm.nl/earss). EARSS collects resistance data of a limited number of invasive bacterial species for the majority of European countries, Israel and Turkey.

We trust that NethMap continues to contribute to our knowledge and awareness regarding the use of antibiotics and the resistance problems which may arise. We thank all who are contributing tot the surveillance efforts of SWAB, and express our hope that they are willing to continue their important clinical and scientific support to SWAB.

The editors:

Prof dr John Degener
Dr ir Mick Mulders

Download from SWAB.nl | 2026-11-12 14:20

Content

Colophon **2**

Preface **6**

1. Summary **8**

2. Samenvatting **10**

3. Use of antimicrobials **12**

4. Resistance among common pathogens **24**

5. Resistance to influenza antiviral drugs **60**

Appendix **65**

Download from SWAB.nl | 2026-11-12 14:20

Summary

NethMap is the annual report of SWAB about the use of antimicrobial agents and the prevalence of resistance to these agents among common human pathogens isolated in the Netherlands. Until recently, this information was restricted to antibacterial agents and bacterial species. NethMap 2008 started publishing data on antimycotic drugs. For the first time, NethMap 2009 is presenting trends in antiviral drug use and resistance in influenza virus.

NethMap's information on antibiotic drug use and development of resistance is based on systematically collected and analysed data over a period from 1996 until now.

Until 2005, the overall use of antimicrobial agents in primary health care remained below 10 defined daily dosages (DDD) per 1000 inhabitants per day. In 2005, there was a light increase in use, 10.5 DDD/1000 inhabitant days, and since then there was a further increase to 11 DDD/1000 inhabitant days in 2008.
The distribution of antibiotic usage over the different drug groups varies per patient population. It is shown that tetracyclines make part of 25% of the usage in general practice, while at the same time tetracyclines are rarely prescribed in hospitals. Nitrofurantoin use has been on the rise in recent years, most probably because of the increased resistance to trimethoprim in *Escherichia coli* in urinary tract infection, which has been reported in SWAB's surveillance system, resulting in subsequent changes in treatment guidelines. Consequently, a decrease is noticed in the use of trimethoprim and sulphonamide.
NethMap 2009 reports a further substitution of amoxicillin by co-amoxiclav and an increase in macrolide and fluoroquinolone use. The background of some of these changes needs further study since they are often not supported by evidence of less effectiveness of the current guidelines. Especially when considering the use of fluoroquinolones, more resistance is encountered, even in the general population.
Amoxicillin, co-amoxiclav and other penicillins account for almost half of all antibiotics used in Dutch hospitals. From 2003, the number of hospital admissions as well as the antibiotic use has increased with 22%. Total use and clinical activities are obviously running in parallel. Between the different groups of antibiotics, however, different trends are recognisable when usage per bed day and usage per admission are compared. When we are observing a growing drug use during a constant number of occupied bed days and also a growing use with a growing number of hospital admissions, we can only conclude that the total use in individual patients is increasing and so does the antibiotic ecological pressure. In NethMap 2009 this is shown to happen for the cephalosporins, carbapenems and glycopeptides. These are all antibiotics prescribed in serious infectious events. For fluoroquinolones the exposure remained almost constant, when compared with 2007.

The use of systemic antimycotic drugs in university medical centres is surpassing six times the use in general hospitals. This is a clear indication of the difference in patient populations between these types of hospitals, the former harbouring a large group of severely immune compromised patients.
New in NethMap 2009 are data on the prescription of antimycobacterial drugs. It is shown that the use of these drugs has changed little over the recent years.
Also new is the introduction of usage data of systemic antiviral drugs. Emerging resistance of influenza viruses may seriously hamper the effectiveness of these drugs during future epidemics.

NethMap 2009 presents data on the prevalence and antimicrobial resistance of *Staphylococcus aureus* in healthy individuals and in patients admitted to nursing homes. In 22% of carriers of *S. aureus* in nursing homes and in 28% of healthy carriers penicillin susceptible *S. aureus* was found. PCR confirmed Methicillin Resistant *S. aureus* (MRSA), was found to be present in only 0.3% of healthy carriers (0.1% of all sampled persons as approximately 30% of the total population is considered *S. aureus* carrier), and in 0.8% in carriers in nursing homes. A large difference in the presence of multiresistant strains was found when healthy persons were compared to nursing home residence, six versus 46% respectively.

Neisseria gonorrhoeae has reached an alarmingly high level of resistance which is still rising. Ciprofloxacin scores a level of 46% resistance in 2008. Third generation cephalosporins, however, are still 100% effective in the Netherlands. In the so-called GRAS project of RIVM the development of resistance of *N. gonorrhoeae* is closely monitored.

Resistance in *Mycobacterium tuberculosis* strains appears to be maintained at the same low level as before.

In 2008, it has been decided by the Netherlands Society of Medical Microbiology (NVMM) and the Society for Infectious Diseases (VIZ) to replace the North American CLSI guidelines for susceptibility testing by the recently developed European guidelines (EUCAST guideline). For a number of antibiotics these guidelines may differ with respect to the interpretation of the laboratory test results, for which so-called breakpoint criteria are set.

Download from SWAB.nl | 2026-11-12 14:20

These differences are based on advancing insights in the relationship between pharmacokinetics and pharmacodynamics (PK/PD) of antimicrobial drugs. In NethMap 2009, the SWAB working group on resistance surveillance has undertaken a comparison study on the resistance data over the past years until 2009, applying the CLSI and EUCAST susceptibility criteria. It is shown that the resistance levels will increase when EUCAST criteria with lower levels of breakpoints for susceptibility are applied. Therefore, in this and future editions of NethMap, higher resistance will be found e.g. for the combination of amoxicillin and clavulanic acid and for the cephalosporins.

In hospitals a gradual rise is seen for resistance in *E. coli* against amoxicillin, co-amoxiclav and first and second generation cephalosporins. Ciprofloxacin reached a critical high of 10% resistance in general hospital departments. In Intensive Care Units a low but steady development of resistance up to 5% can be seen for third generation cephalosporins in *Klebsiella pneumoniae.* The role of spread of strains producing Extended Spectrum Beta-Lactamases (ESBL's) remains to be confirmed. Even so in Intensive Care units a gradual increase of multiresistant *S. aureus* is seen against quinolones, macrolides, aminoglycosides. The prevalence of MRSA is low but when methicillin resistance and multiresistance to other antibiotic groups are combined, the alternative ways of treatment may become seriously hampered. However, vancomycin resistance in *S.aureus* is rarely encountered in the Netherlands and not yet reported in NethMap. Vancomycin is still the rescue drug for resistant *S.aureus* infection.
More animal husbandry related MRSA isolates were detected in 2008 than before.

Data on pneumococci and *Haemophilus influenzae* were collected in hospitals. For the majority of these strains it can, by the nature of such public health-related species, be suggested that these are community-acquired rather than hospital-acquired. Their resistance profiles may be a reflection of the situation in the general population. Therefore, it is of interest that in *Haemophilus influenzae* an increase of resistance to amoxicillin as well as to co-amoxiclav is observed. The increase is clearly not due to a rise in beta lactamase producing strains, therefore indicating an increasing prevalence of so called Beta Lactamase Negative Amoxicillin Resistant (BLNAR) strains. Doxycycline is still a reasonable alternative choice to combat infections with BLNAR *Haemophilus influenzae.*
In pneumococci, resistance against macrolides has risen in 2008 to a critical high of > 10% and tetracycline resistance parallels this development.
We can conclude that, in general and on the basis of these and many more data presented in NethMap 2009, we can not be too optimistic about the situation of the emergence of antibiotic resistance in the Netherlands, while at the same time we are still better off than many countries surrounding us in Europe, according to data of the European Antimicrobial Resistance Surveillance System (EARSS: www.rivm.nl/earss/).

Download from SWAB.nl | 2026-11-12 14:20

Samenvatting.

NethMap is het jaarlijkse rapport van de SWAB over het gebruik van antimicrobiële middelen en resistentie in de meest voorkomende, voor de mens pathogene, micro-organismen in Nederland. Tot voor kort beperkte deze informatie zich tot antibiotica en bacteriesoorten. In 2008 werd NethMap aangevuld met gegevens over middelen tegen schimmelinfecties en in de voor u liggende NethMap 2009 zijn nu voor het eerst ook trends in resistentie bij influenzavirus tegen antivirale middelen te vinden.
De data in NethMap zijn gebaseerd op systematisch verzamelde en bewerkte gegevens over antimicrobiële middelen en de ontwikkeling in resistentie daartegen.

Het gebruik van antibiotica in de Nederlandse eerstelijns gezondheidszorg is tot 2005 steeds onder de 10 standaard dagdoseringen (DDDs) per 1000 inwoners per dag gebleven. In 2005 was het gebruik iets hoger, 10,5 DDD/1000 inwoner-dagen, en het is sindsdien licht verder gestegen tot 11 DDD/1000 inwoner-dagen in 2008. De verdeling van het gebruik van antibiotica uit de verschillende groepen verschilt van die in het ziekenhuis. Zo is te zien dat tetracyclines 25% uitmaken van het gebruik buiten het ziekenhuis, terwijl deze middelen intramuraal slechts zelden worden toegepast. Het gebruik van nitrofurantoïne was al langere tijd aan het stijgen. Waarschijnlijk kwam dit door de toegenomen resistentie tegen trimethoprim bij urineweginfecties en, als reactie daarop en mede ten gevolge van de resultaten van de SWAB surveillance, de aanpassingen in de richtlijnen voor huisartsen. We zien dan ook een gelijktijdige daling van het trimethoprim en sulfonamide gebruik optreden. Wat elk jaar weer opvalt in NethMap is de toenemende vervanging van amoxicilline door de combinatie van amoxicilline met de beta-lactamase remmer clavulaanzuur.
Verder zien we een toenemend gebruik van macroliden en fluorochinolonen.
Het toenemend gebruik van co-amoxiclav en fluoro-chinolonen dient onderbouwd te worden, omdat gegevens over een grotere effectiviteit van deze middelen in de huisartspopulatie ontbreken. Gelet op de verder toenemende resistentie voor ciprofloxacine is sprake van een zorgwekkende ontwikkeling.

Bijna de helft van het antibioticagebruik in ziekenhuizen bestaat uit amoxicilline, al of niet in combinatie met de beta-lactamaseremmer clavulaanzuur, en andere penicillines.
Vanaf 2003 is zowel het aantal ziekenhuisopnames als het antibioticagebruik in DDD's gestegen met 22%. Het totale gebruik en de klinische activiteiten houden klaarblijkelijk gelijke pas. Tussen de verschillende groepen antibiotica zijn daarentegen verschillende trends zichtbaar als gebruik per opname en gebruik per beddag in ogenschouw worden genomen. Zien we bij hetzelfde aantal beddagen een toename van het aantal opnames en voor beide parameters een toenemend gebruik dan is er een duidelijke stijging van de expositie aan antibiotica. Dit is met name waargenomen bij cefalosporines, carbapenems en glycopeptiden, middelen die in ernstige situaties worden voorgeschreven. Voor chinolonen bleef de expositie nagenoeg constant vergeleken met 2007.

Het gebruik van systemische antimycotica ligt in universitaire centra tot 6 maal hoger dan in andere ziekenhuizen, hetgeen het verschil in patiëntenpopulaties weergeeft.
Nieuw zijn de gegevens over de toepassing van middelen tegen infecties door mycobacteriën. Over de jaren heen is het gebruik weinig verschillend.
Ook nieuw is de toevoeging van gebruiksgegevens van systemische antivirale middelen. De verschillen tussen universitaire centra en andere ziekenhuizen zijn opvallend. De zich ontwikkelende resistentie bij influenza virussen vormt een bedreiging voor de effectiviteit van de antivirale middelen.

NethMap 2009 toont gedetailleerde gegevens over de gevoeligheid voor antibiotica van *Staphylococcus aureus* bij gezonde personen buiten het ziekenhuis en bij bewoners van verpleeghuizen. Bij 22% van de dragers onder bewoners van verpleeghuizen en bij 28% van de gezonde dragers werd voor penicilline gevoelige *S. aureus* aangetroffen. Meticilline resistente *S. aureus* (MRSA), bevestigd met PCR van het *mec*A resistentiegen, werd aangetroffen bij slechts 0,3% van de gezonde dragers (0,1% van alle bemonsterde personen, want het totaal percentage dragers onder een normale bevolking is ongeveer 30%) en bij 0,8% van de bewoners van verpleeghuizen. Een groot verschil in dragerschap van multiresistente *S. aureus* werd gevonden tussen gezonde personen en bewoners van verpleeghuizen, 6% en 46% respectievelijk.
De resistentie bij *Neisseria gonorrhoeae* heeft een verontrustend hoog niveau dat nog steeds toeneemt. Ciprofloxacine heeft een resistentie percentage van 46 bereikt. Derde generatie cefalosporines zijn nog wel werkzaam tegen gonokokken. In het zgn. GRAS project wordt de resistentieontwikkeling van gonokokken nauwlettend in de gaten gehouden.
Resistentie van *Mycobacterium tuberculosis* stammen blijkt zich op hetzelfde niveau te handhaven als in vorige jaren.

In 2008 is o.a. door de Nederlandse Vereniging voor Medische Microbiologie (NvMM) en de Vereniging voor Infectieziekten (VIZ) besloten om voor de interpretatie

Download from SWAB.nl | 2026-11-12 14:20

van gevoeligheidsbepalingen de N. Amerikaanse richtlijn (CLSI) te vervangen door de nieuwe Europese (EUCAST) criteria. Omdat voor een aantal antibiotica de Europese criteria kunnen verschillen, hetgeen te maken heeft met voortschrijdend inzicht in de relatie tussen farmacokinetiek en farmacodynamiek (PK/PD), is in deze editie van NethMap door de werkgroep resistentiesurveillance een vergelijking gemaakt tussen de uitkomsten van de bepalingen bij hantering van beide sets criteria. Het valt daarbij op dat voor sommige groepen antibiotica de gevoeligheidspercentages met EUCAST lager uitvallen en er dus meer resistentie gevonden wordt dan met de Amerikaanse CLSI criteria. Dit is bij voorbeeld opmerkelijk bij de combinatie amoxicilline en clavulaanzuur en bij de cefalosporines.

In NethMap 2009 zien we in het ziekenhuis een geleidelijke stijging van de resistentie van *E. coli* tegen amoxicilline, amoxicilline-clavulaanzuur en eerste en tweede generatie cefalosporines. Ciprofloxacine vertoont een stijgende lijn en heeft de grens van 10% bereikt op algemene afdelingen.
Op Intensive Cares zien we een langzame toename van ceftazidim resistente *Klebsiella pneumoniae* tot 5%. Studies zij in gang om vast te stellen in hoeverre de verspreiding van Extended Spectrum Beta-lactamase (ESBL) producerende bacteriestammen hierbij een rol speelt.
We zien voorts een geleidelijke toename van resistentie van *S.aureus* op Intensive Cares voor meerdere groepen antibiotica, chinolonen, macroliden, aminoglycosiden en in geringere mate van MRSA. Feit is dat hiermee de mogelijkheid van alternatieve behandeling, b.v. bij een MRSA infectie afneemt. Problemen met glycopeptide resistentie zijn niet waargenomen bij *S. aureus*. Dit laatste vormt wel een reëel probleem bij infecties met enterokokken. In 2008 zien we een verdere toename van het aantal MRSA isolaten dat vee-gerelateerd is.
In de ziekenhuizen zijn gegevens verzameld van pneumokokken en *Haemophilus influenzae.* Deze bacteriesoorten zullen in het overgrote deel community-acquired zijn en hun resistentieprofielen zullen daarom waarschijnlijk ook een redelijke afspiegeling vormen van de stammen buiten het ziekenhuis. Opmerkelijk is de toename van resistentie bij *Haemophilus* tegen zowel amoxicilline als amoxicilline met clavulaanzuur. Dit is een aanwijzing voor de verspreiding van zogenaamde Beta-Lactamase Negatieve Amoxicilline Resistente (BLNAR) stammen. Doxycycline is nog een redelijk alternatief bij dit type resistente *Haemophilus*.
Bij pneumokokken zet de macrolideresistentie door tot > 10% in 2008, ongeveer gelijk opgaand met resistentie tegen tetracyclines.

Al met al kan geen optimistisch beeld gegeven worden van de zich ontwikkelende resistentieproblematiek in Nederland, terwijl de situatie in vergelijking met vele andere ons omringende landen nog vrij gunstig is, wanneer we deze en de nog vele andere in deze NethMap 2009 gepresenteerde data vergelijken met die van het European Antimicrobial Resistance Surveillance System (EARSS: www.rivm.nl/earss/).

Download from SWAB.nl | 2026-11-12 14:20

3. Use of antimicrobials

This chapter of the report considers the use of antimicrobial agents in human medicine only. Data on the use of such agents in animal husbandry and veterinary medicine are reported elsewhere (1).
Human consumption is presented in two parts. One part describes the prescription and use of antibiotics in the community, also termed "Primary Health Care". About 85% of antibiotic use in primary health care is prescribed by general practitioners (2). The second part presents surveillance data on total hospital consumption of antimicrobial agents in acute care hospitals in the Netherlands. Details regarding the structural acquisition and analysis of these consumption data are presented in the Appendix (section "Materials and Methods").

Primary health care

Use of antibiotics

Over the past 10 years the overall use of antibiotics for systemic use in primary health care remained rather constant. From 1999-2004, usage was 10 DDD/1000 inhabitant-days (table 1). Over the past four years, use gradually increased to 11 DDD/1000 inhabitant-days. The distribution of antibiotics by class in 2008 is presented in figure 1. Tetracyclines (mainly doxycycline) represented 25% of total antibiotic use in primary health care. Other frequently used antibiotics were penicillins with extended spectrum (mainly amoxicillin), combinations of penicillins with beta-lactamase inhibitors (essentially co-amoxiclav) and macrolides, each representing 17%, 15% and 13% of the total use respectively.
The use of amoxicillin slightly decreased from 2.11 in 1997 to 1.91 DDD/1000 inhabitant-days in 2008 (– 9%) with small fluctuations across years, while the use of co-amoxiclav increased from 0.91 in 1997 to 1.71 DDD/1000 inhabitant-days in 2008, which means an increase of 93% (table 1; figure 2).
The use of macrolides increased from 1.11 in 1997 to 1.36 DDD/1000 inhabitant-days in 2008 (+ 22%; table 1). The use of subgroups of macrolides is presented in figure 3. Clarithromycin was the most commonly used macrolide. Its use slightly increased from 0.65 in 1997 to 0.90 in 2005 and subsequently slightly decreased to

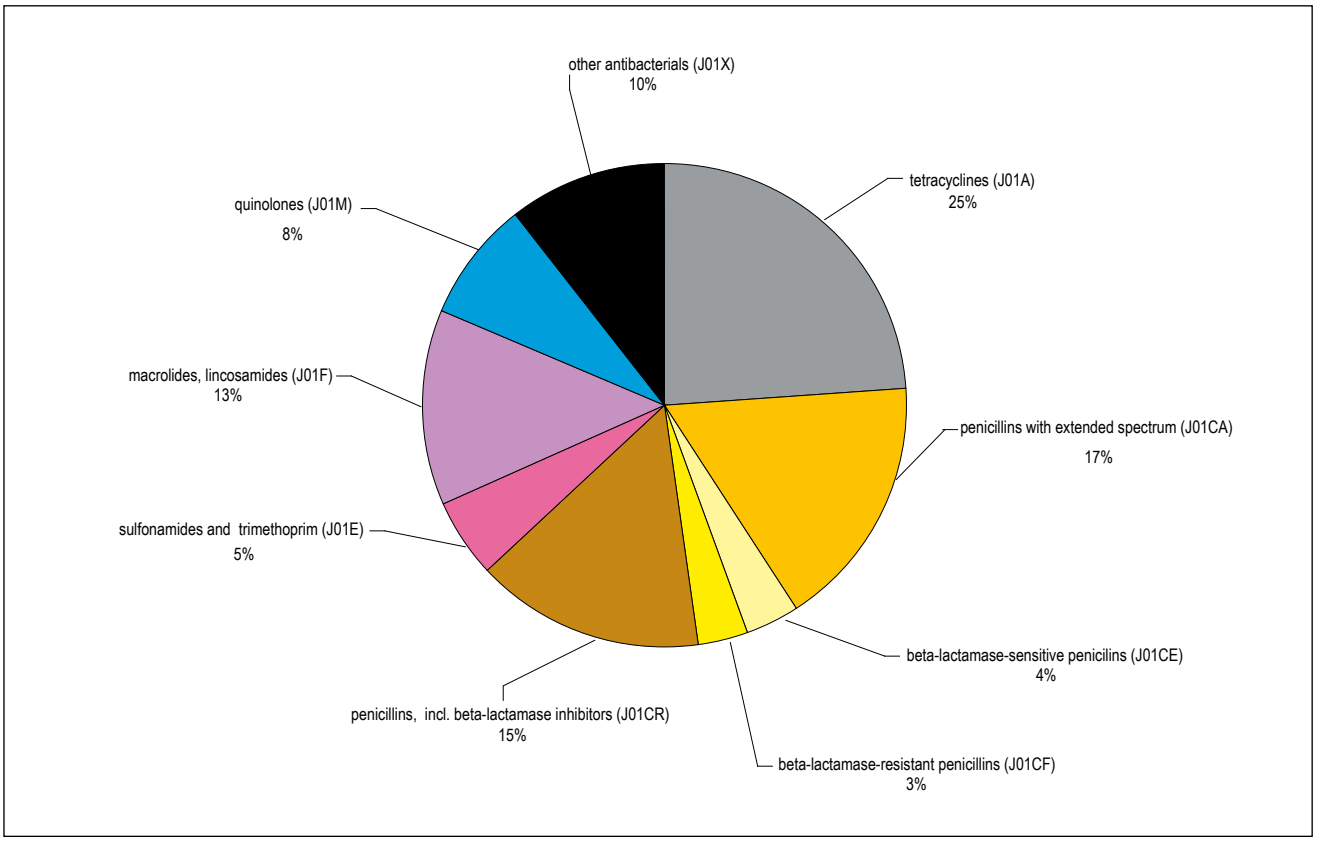


Figure 1. Distribution of the use of antibiotics for systemic use in primary health care, 2008 (SFK).

Download from SWAB.nl | 2026-11-12 14:20

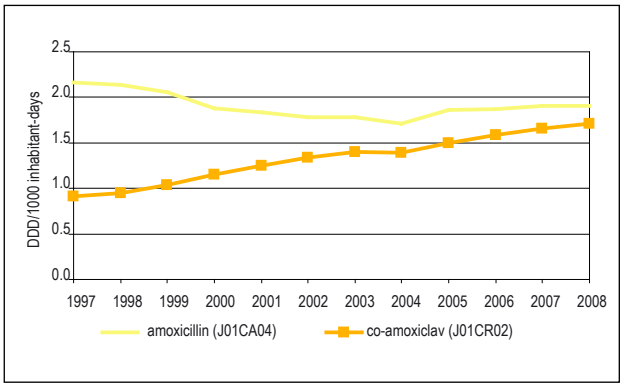


Figure 2. Use of amoxicillin and co-amoxiclav in primary health care, 1997-2008 (SFK).

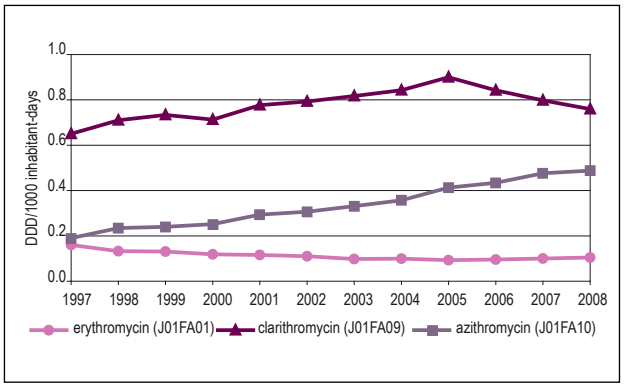


Figure 3. Use of macrolides for systemic use in primary health care, 1997-2008 (SFK).

Table 1. 10-years data on the use of antibiotics for systemic use (J01) in primary care (DDD/1000 inhabitant-days), 1999-2008 (Source: SFK)

ATC Group	Therapeutic group	year									
		1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
J01AA	Tetracyclines	2,49	2,48	2,40	2,34	2,24	2,24	2,41	2,37	2,57	2,66
J01CA	Penicillins with extended spectrum	2,05	1,88	1,83	1,78	1,78	1,71	1,86	1,87	1,91	1,91
J01CE	Beta-lactamase sensitive penicillins	0,52	0,52	0,49	0,46	0,44	0,43	0,44	0,50	0,46	0,42
J01CF	Beta-lactamase resistant penicillins	0,23	0,24	0,25	0,25	0,27	0,28	0,29	0,31	0,32	0,36
J01CR	Penicillins + beta-lactamase-inhibitors	1,04	1,15	1,25	1,34	1,40	1,39	1,50	1,59	1,66	1,71
J01D	Cephalosporins	0,10	0,08	0,07	0,07	0,06	0,05	0,05	0,04	0,05	0,04
J01EA	Trimethoprim and derivatives	0,30	0,28	0,28	0,27	0,27	0,26	0,25	0,23	0,22	0,21
J01EC	Intermediate-acting sulphonamides	0,00	0,00	0,00	0,01	0,00	0,00	0,00	0,00	0,00	0,00
J01EE	Sulphonamides + trimethoprim	0,46	0,43	0,42	0,40	0,40	0,39	0,38	0,37	0,36	0,36
J01FA	Macrolides	1,17	1,14	1,23	1,24	1,27	1,32	1,42	1,39	1,39	1,36
J01FF	Lincosamides	0,04	0,04	0,05	0,06	0,06	0,07	0,08	0,09	0,10	0,11
J01GB	Aminoglycosides	0,00	0,00	0,01	0,01	0,02	0,02	0,02	0,03	0,03	0,03
J01MA	Fluoroquinolones	0,85	0,80	0,80	0,78	0,79	0,83	0,84	0,87	0,91	0,89
J01MB	Other quinolones	0,04	0,04	0,04	0,03	0,03	0,02	0,02	0,02	0,02	0,02
J01XB	Polymyxins	0,02	0,02	0,02	0,02	0,02	0,02	0,02	0,00	0,00	0,00
J01XE	Nitrofuran derivatives	0,64	0,68	0,72	0,74	0,78	0,81	0,90	1,00	1,07	1,13
J01XX05	Methenamine	0,06	0,06	0,06	0,04	0,03	0,02	0,02	0,03	0,03	0,02
J01	Antibiotics for systemic use (total)	10,02	9,86	9,92	9,83	9,86	9,87	10,51	10,73	11,10	11,24

* From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Download from SWAB.nl | 2026-11-12 14:20

0.76 DDD/1000 inhabitant-days in 2008. The use of azithromycin doubled between 1997 and 2008. The use of erythromycin slightly decreased over the past years. Total use of the fluoroquinolones increased from 0.77 in 1997 to 0.89 DDD/1000 inhabitant-days in 2008 (+ 15%; table 1, figure 4), within which the use of ciprofloxacin more than doubled. Since 2002, ciprofloxacin is the fluoroquinolone used most commonly. The use of norfloxacin and ofloxacin decreased during these years. The use of moxifloxacin almost equals the use of levofloxacin in 2008.

The use of nitrofurantoin increased from 0.59 in 1997 to 1.13 DDD/1000 inhabitant-days in 2008 whereas the use of sulfonamides and trimethoprim (J01 EA and EE combined) decreased (– 22%, table 1).

Use of antimycobacterials

Between 1998 and 2007, the use of antimycobacterials in primary health care remained rather constant (table 2). Isoniazid is the most prescribed antimycobacterial

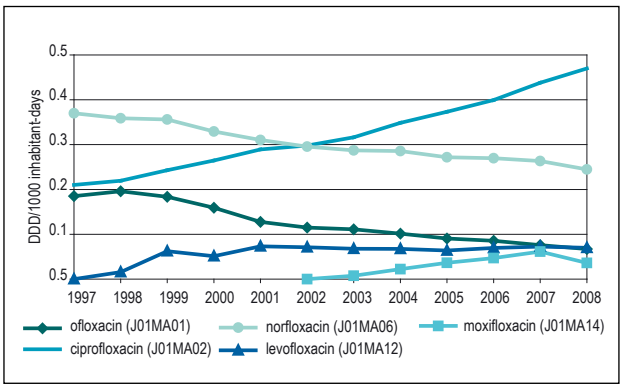


Figure 4. Use of quinolones for systemic use in primary health care, 1997-2008 (Source: SFK).

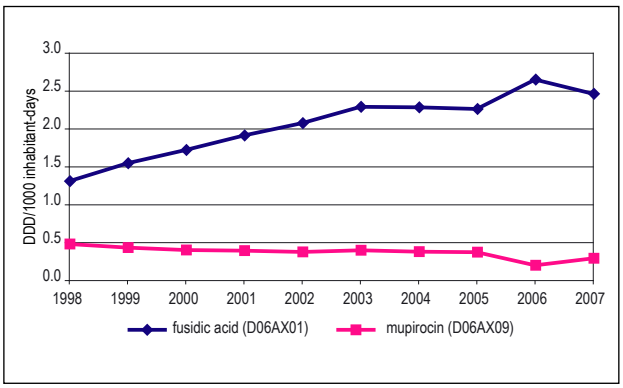


Figure 5. Use of fusidic acid and mupirocin in primary health care, 1998-2007 (Source: SWAB).

Table 2. 10-years data on the use of antimycobacterial drugs in primary care ((DDD/1000 inhabitant-days), 1998-2007 (Source: SFK)

ATCGroup	Antimycobacterials	year									
		1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
J04AB02	Rifampicin	0,05	0,06	0,06	0,06	0,06	0,05	0,05	0,05	0,05	0,06
J04AC01	Isoniazid	0,11	0,12	0,10	0,10	0,10	0,09	0,09	0,09	0,09	0,09
J04AK01	Pyrazinamide	0,02	0,03	0,03	0,03	0,02	0,02	0,02	0,02	0,02	0,02
J04AK02	Ethambutol	0,03	0,03	0,03	0,03	0,03	0,03	0,02	0,02	0,02	0,02
J04AM02	Rifampicin and isoniazid	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01
J04BA02	Dapsone	0,10	0,10	0,09	0,08	0,08	0,09	0,09	0,09	0,09	0,09

Table 3. 10-years data on the use of antimicrobials and chemotherapeutics for dermatological use in primary care ((DDD/1000 inhabitant-days), 1998-2007 (Source: SFK)

ATC Group	Drugs	year									
		1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
D06AA04	Tetracycline	0,04	0,04	0,03	0,03	0,03	0,03	0,03	0,03	0,04	0,03
D06AX01	Fusidic acid	1,31	1,55	1,72	1,91	2,08	2,29	2,29	2,26	2,65	2,46
D06AX09	Mupirocin	0,48	0,43	0,40	0,39	0,38	0,40	0,38	0,37	0,20	0,29
D06BA01	Silver sulfadiazine	1,24	1,32	1,25	1,25	1,23	1,27	1,17	1,11	1,15	1,15
D06BB03	Acyclovir	0,18	0,14	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
D06BB04	Podophyllotoxin	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01
D06BX01	Metronidazole	0,38	0,44	0,50	0,56	0,60	0,61	0,64	0,67	0,68	0,75

Download from SWAB.nl | 2026-11-12 14:20

followed by rifampicin. The use of ethambutol equals the use of pyrazinamide.

Use of antibiotics and chemotherapeutics for dermatological use

The use of fusidic acid increased from 1.31 DDD/1000 inhabitant-days in 1998 to 2.46 in 2007 (table 3, figure 5). The use of silver sulfadiazine slightly decreased. Since 2000, no use of topical acyclovir was registered. The use of metronidazole increased from 0.38 in 1998 to 0.75 DDD/1000 inhabitant-days in 2007.

Discussion

The antibiotic consumption in primary health care remained constant at 10 DDD/1000 inhabitant-days until 2004. From 2005 to 2008 the consumption gradually increased to 11 DDD/1000 inhabitant-days and was slightly increased compared to previous years. However, the use of antibiotics is still low if compared with other European countries (3).

In the past 10 years the use of penicillines with beta-lactamase inhibitors, macrolides and fluoroquinolones increased, whereas the use of penicillins with extended spectrum and sulfonamides and trimethoprim decreased. This international trend of declining use of narrower spectrum and of prescribing more broad-spectrum and newer chemotherapeutics has been described from 1991 for the Netherlands (4), whereas these drugs generally have a broader antimicrobial spectrum than necessary (5).

The remarkable increase in the use of nitrofurantoin may be explained by the national guidelines of the Dutch College of General practitioners (NHG) (6) that have been changed over the years with regard to the pharmacotherapy of urinary tract infections. In 2005 these guidelines were revised and nitrofurantoin was classified as the drug of first choice (5 days treatment) because of lower resistance levels. Trimethoprim is nowadays ranked as a urinary tract infection antibiotic of second choice.

Moreover, subtle shifts in the patterns of use within the various classes of antibiotics are observed. The increased use of ciprofloxacin seems to be offset by a decrease in ofloxacin and norfloxacin. Also, within the class of the macrolides a shift from erythromycin to the newer macrolides as clarithromycin and azithromycin was observed. This trends may be relevant in the face of growing rates of resistance among common pathogens and therewith the rate of treatment failures.

The relative use of the antimycobacterials seems to be in line with the general principles of the treatment and prophylaxis of tuberculosis. The constant use of these drugs over the years is suggestive for limited resistance problems over the past years.

To better understand the topical use of fusidic acid and mupirocin, an in-depth analysis of indications is warranted. Since topical acyclovir is nowadays an over-the-counter drug, usage is no longer registered by the community pharmacies.

Download from SWAB.nl | 2026-11-12 14:20

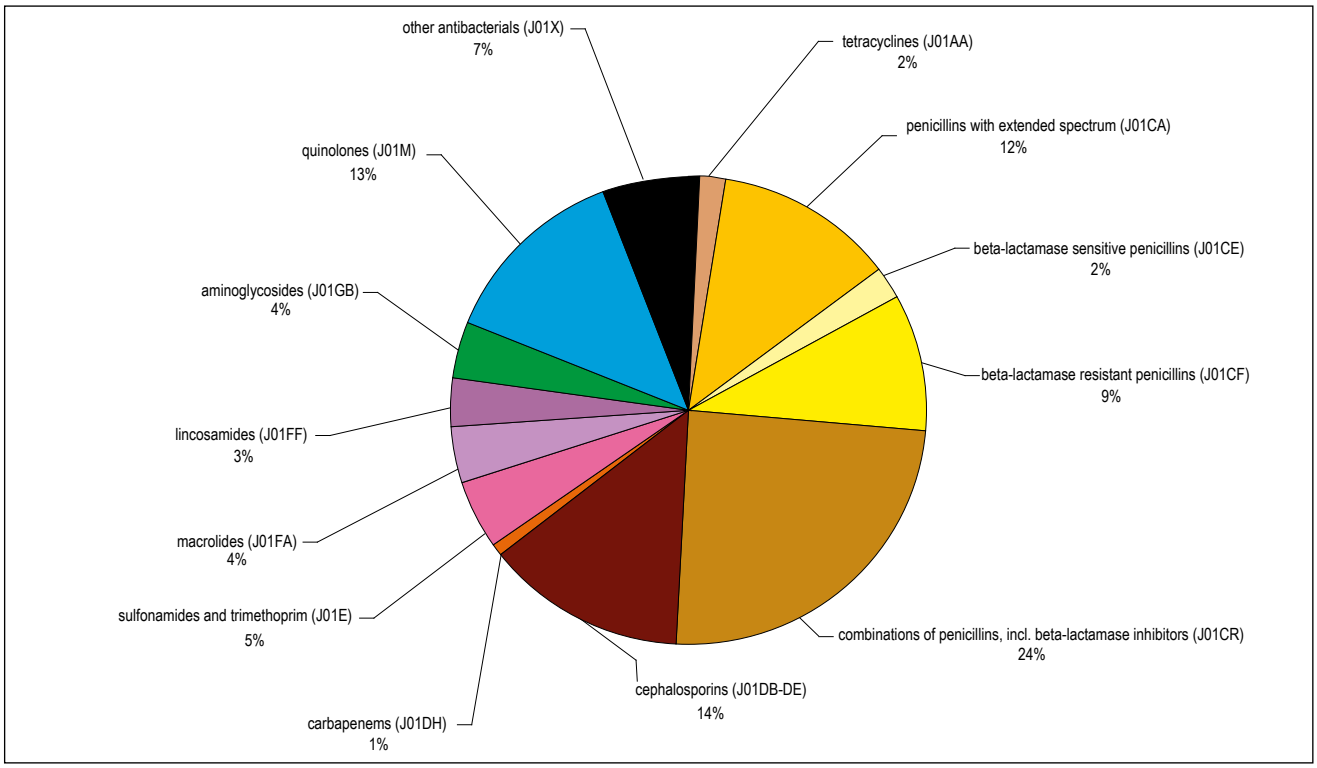


Figure 6. Distribution of the use of antibiotics for systemic use in hospitals, 2007 (Source: SWAB)

Table 4. Use of antibiotics for systemic use (J01) in hospitals (DDD/100 patient-days), 2003-2007 (Source: SWAB).

ATC groupa	Therapeutic group	2003	2004	2005	2006	2007
J01AA	Tetracyclines	1,4	1,5	1,6	1,6	1,4
J01CA	Penicillins with extended spectrum	6,0	6,0	6,7	7,6	7,3
J01CE	Beta-lactamase sensitive penicillins	1,2	1,4	1,4	1,4	1,2
J01CF	Beta-lactamase resistant penicillins	5,4	5,7	5,8	5,9	5,6
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	12,1	12,8	13,9	15,1	14,0
J01DB -DE	Cephalosporins	6,5	7,0	7,4	8,4	8,4
J01DF	Monobactams	0,0	0,0	0,0	0,0	0,0
J01DH	Carbapenems	0,5	0,5	0,6	0,6	0,8
J01EA	Trimethoprim and derivatives	0,5	0,4	0,6	0,8	0,5
J01EC	Intermediate-acting sulfonamides	0,1	0,1	0,0	0,0	0,1
J01EE	Combinations of sulfonamides and trimethoprim, including derivatives	2,3	2,1	2,3	2,1	2,3
J01FA	Macrolides	2,4	2,3	2,8	2,5	2,7
J01FF	Lincosamides	1,6	1,8	1,9	2,0	2,1
J01GB	Aminoglycosides	2,5	2,2	2,6	2,5	2,5
J01MA	Fluoroquinolones	6,4	6,5	7,3	8,0	7,6
J01MB	Other quinolones	0,1	0,1	0,1	0,1	0,0
J01XA	Glycopeptides	0,5	0,6	0,8	0,7	1,0
J01XB	Polymyxins	0,1	0,1	0,2	0,2	0,1
J01XC	Steroid antibacterials (fusidic acid)	0,0	0,0	0,0	0,0	0,0
J01XD	Imidazole derivatives	1,6	1,7	1,5	1,7	1,8
J01XE	Nitrofuran derivatives	0,7	0,9	1,0	1,0	1,1
J01XX05	Methenamine	0,0	0,0	0,0	0,0	0,0
J01XX08	Linezolid	0,0	0,0	0,0	0,0	0,0
J01	Antibiotics for systemic use (total)	51,9	53,8	58,3	62,2	60,9

a) From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Download from SWAB.nl | 2026-11-12 14:20

Hospitals

Hospital resource indicators

The average number of beddays per hospital in our cohort increased from 132,964 in 2003 to 141,413 in 2007 (+ 6.4%). The average number of admissions however increased even more from 17,910 in 2003 to 21,741 in 2007 (+ 21%). The average length of stay in these hospitals has therefore decreased from 7.4 to 6.5 days (– 13%).

Hospital use of antibiotics

Data on antibiotic use are expressed in DDD per 100 patient-days as well as in DDD per 100 admissions, because trends over time in both units of measurement do not always correlate (tables 4 and 5).
The total systemic use of antibiotics in our cohort of hospitals was 61 DDD per 100 patient-days in 2007, an increase of 17% compared to the total systemic use in 2003, which was 51 DDD per 100 patient-days. The number of patient-days increased slightly (+ 4%), while the average number of DDD per hospital increased from 59,666 in 2003 to 72,826 in 2007 (+ 22%).
The number of DDD per 100 admissions has remained practically the same, 336.2 DDD/100 admissions in 2003 and 335.0 DDD/100 admissions in 2007.
Both the number of patients as the DDD per hospital increased with almost 22%, therefore the mean antibiotic use per patient remained constant.
Four main categories with regard to trends in antibiotic use over the years could be distinguished (tables 4 and 5).

1. Increase in both units of measurement
For cephalosporins, carbapenems, lincosamides, glycopeptides and nitrofurantoin an increase in DDD per 100 patient-days as well as DDD per 100 admissions was observed. Even though the average patient was admitted to the hospital for a shorter period of time, they used more antibiotics than before.

2. Increase in DDD per 100 patient-days, constant DDD per 100 admissions
Penicillins with extended spectrum, combinations of penicillins (incl. beta-lactamase inhibitors), macrolides, and fluoroquinolones showed an increase in DDD per 100 patient-days, while the DDD per 100 admissions remained more or less constant. This implies that the

Table 5. Use of antibiotics for systemic use (J01) in hospitals (DDD/100 admissions), 2003-2007 (Source: SWAB).

ATC-groupa	Therapeutic group	2003	2004	2005	2006	2007
J01AA	Tetracyclines	8,8	8,4	8,8	8,7	7,7
J01CA	Penicillins with extended spectrum	38,6	34,3	36,4	41,0	40,3
J01CE	Beta-lactamase sensitive penicillins	7,8	7,8	7,5	7,7	6,8
J01CF	Beta-lactamase resistant penicillins	34,6	33,0	31,4	31,8	31,0
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	77,7	73,1	75,4	81,7	77,3
J01DB-DE	Cephalosporins	42,0	39,4	39,8	45,3	46,3
J01DF	Monobactams	0,0	0,0	0,0	0,0	0,0
J01DH	Carbapenems	3,3	2,8	3,2	3,0	4,4
J01EA	Trimethoprim and derivatives	3,1	2,3	3,0	4,2	2,9
J01EC	Intermediate-acting sulfonamides	0,8	0,3	0,3	0,1	0,4
J01EE	Combinations of sulfonamides and trimethoprim, including derivatives	14,4	12,1	12,2	11,5	12,7
J01FA	Macrolides	15,4	13,4	15,1	13,4	14,8
J01FF	Lincosamides	10,2	10,2	10,5	10,8	11,5
J01GB	Aminoglycosides	15,8	12,5	13,9	13,7	14,0
J01MA	Fluoroquinolones	41,0	37,2	39,7	43,3	41,9
J01MB	Other quinolones	0,6	0,8	0,5	0,3	0,2
J01XA	Glycopeptides	3,4	3,5	4,1	3,9	5,3
J01XB	Polymyxins	0,5	0,6	1,1	0,9	0,7
J01XC	Steroid antibacterials (fusidic acid)	0,2	0,1	0,2	0,1	0,1
J01XD	Imidazole derivatives	10,1	9,6	7,9	9,0	9,9
J01XE	Nitrofuran derivatives	4,7	4,9	5,6	5,2	6,2
J01XX05	Methenamine	0,2	0,4	0,1	0,1	0,1
J01XX08	Linezolid	0,1	0,1	0,2	0,2	0,2
J01	Antibiotics for systemic use (total)	333,2	306,8	316,9	335,9	335,0

a) From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Download from SWAB.nl | 2026-11-12 14:20

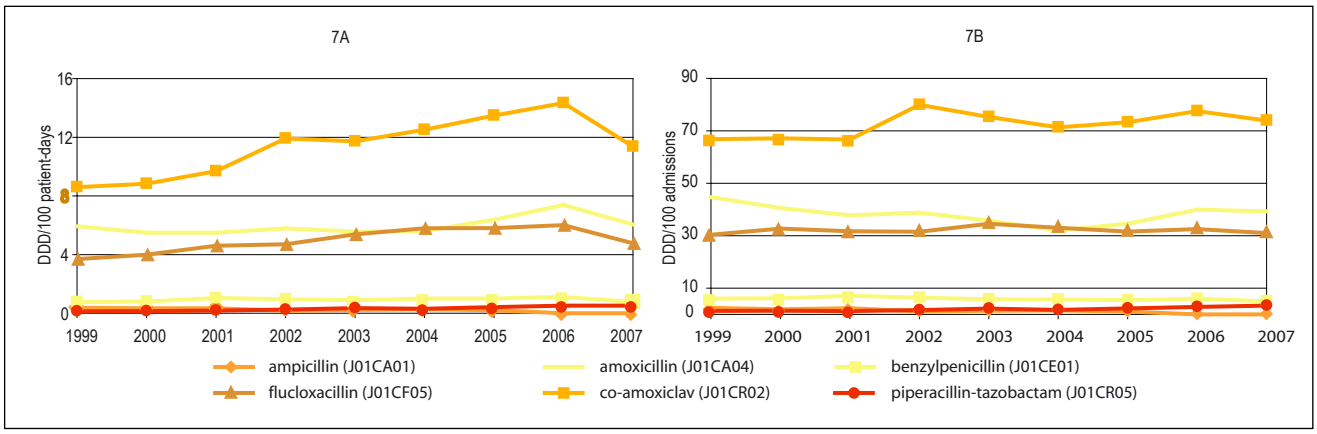


Figure 7. Use of penicillins in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B).

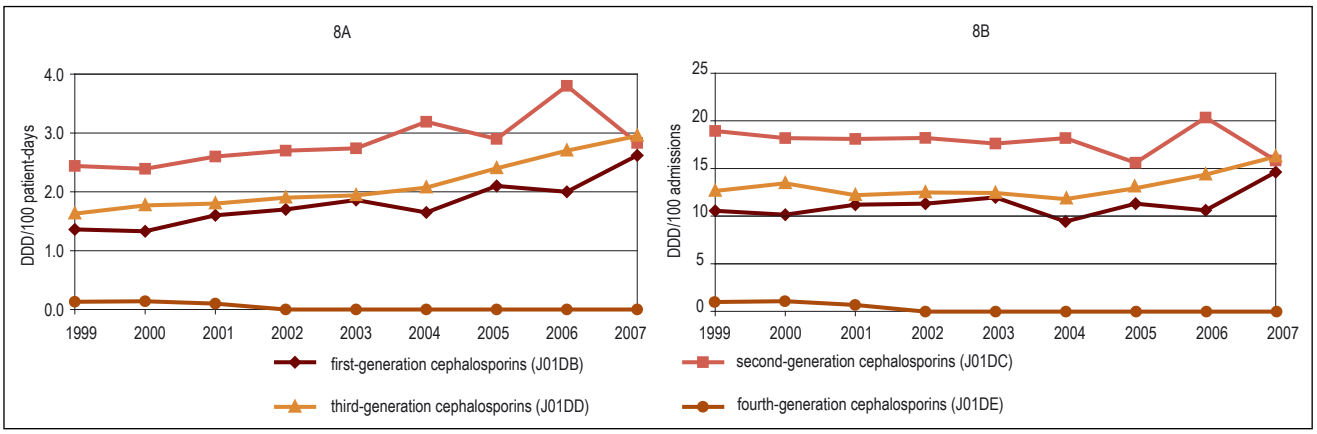


Figure 8. Use of cephalosporins in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B).

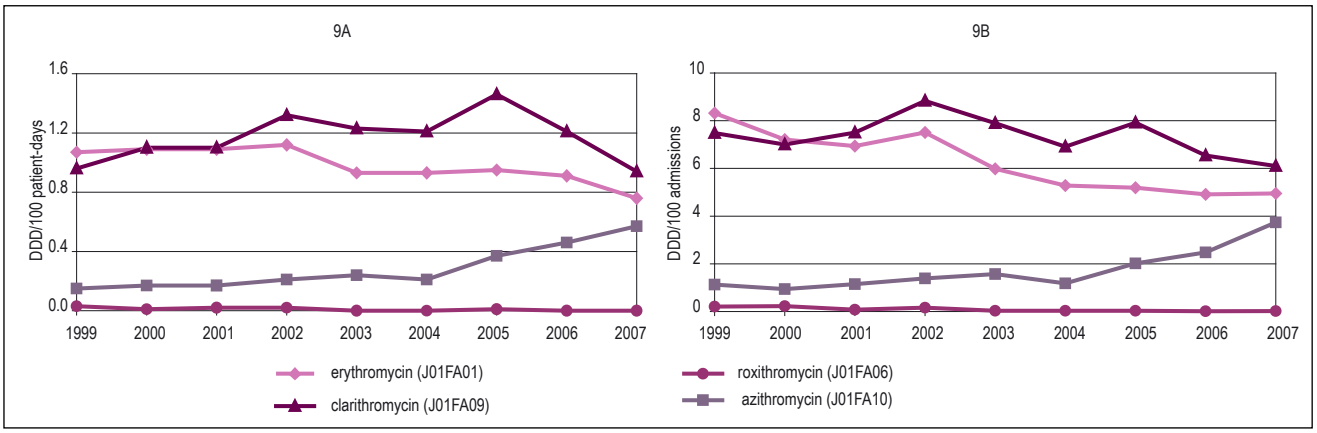


Figure 9. Use of macrolides in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B).

average patient was exposed to the same number of doses. However, since more patients were admitted to the hospital, a significant increase in antibiotic use per ward/hospital was observed.

3. Constant number of DDD per 100 patient-days, decrease in DDD per 100 admissions

For tetracyclines, beta-lactamase sensitive penicillins, beta-lactamase resistant penicillins, combinations of sulphonamides and trimethoprim and quinolones (except fluoroquinolones), the DDD per 100 patient-days remained constant, but the DDD per 100 admissions decreased. The average patient used less antibiotics, during a shorter stay in the hospital. Due to the increase in admissions, the relative use per ward/hospital remained constant.

Download from SWAB.nl | 2026-11-12 14:20

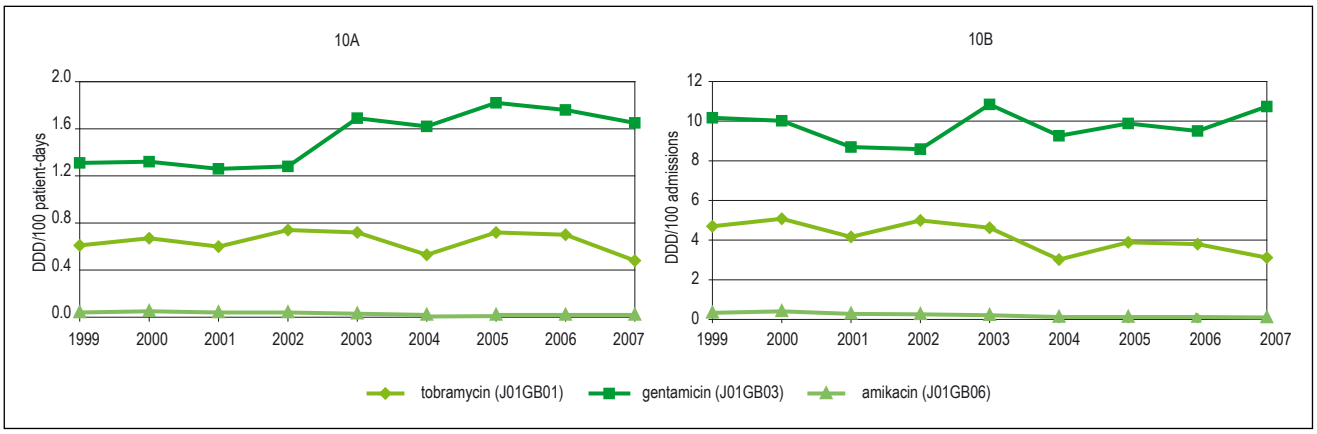


Figure 10. Use of aminoglycosides in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B).

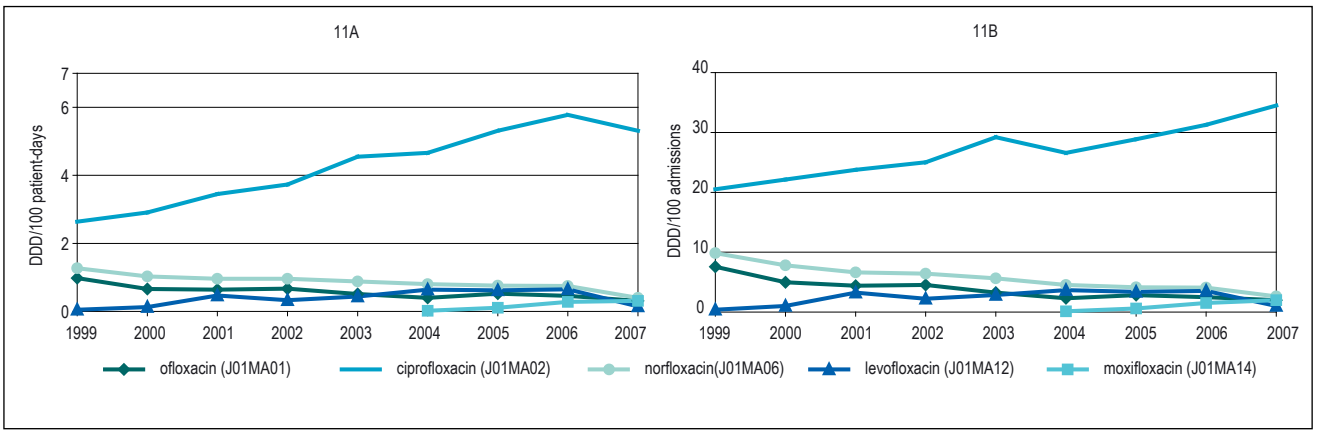


Figure 11. Use of fluoroquinolones in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B).

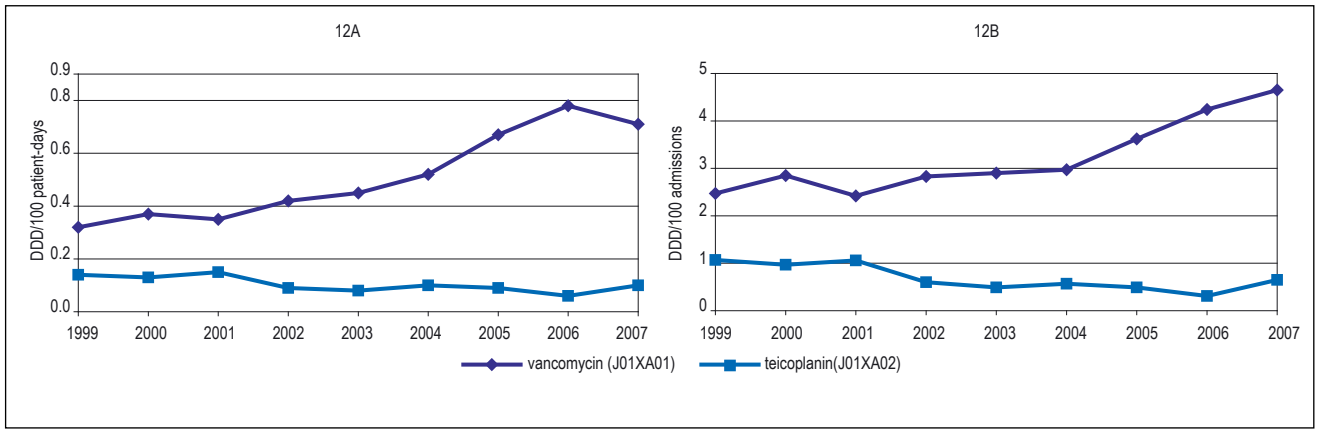


Figure 12. Use of glycopeptides in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B).

4. Constant number of both DDD per 100 patient-days and DDD per 100 admissions

Trimethoprim and derivatives and aminoglycosides showed a constant DDD per 100 patient-days as well as DDD per 100 admissions. This implies that the use of these antibiotics decreased significantly in the average patient. This might be due to a reduction of the number of doses per patient as well as a reduction in the exposed number of patients, or a combination of both.

Figure 6 depicts the distribution of use of antibiotics per class in 2007. The relative use of the different subclasses of antibiotics remained constant over the past years (data not shown).

The relative use of penicillins was approximately 47%. The largest proportion (24%) consisted of the combination of penicillins, including beta-lactamase inhibitors, mainly co-amoxiclav (figures 7A and B).

Download from SWAB.nl | 2026-11-12 14:20

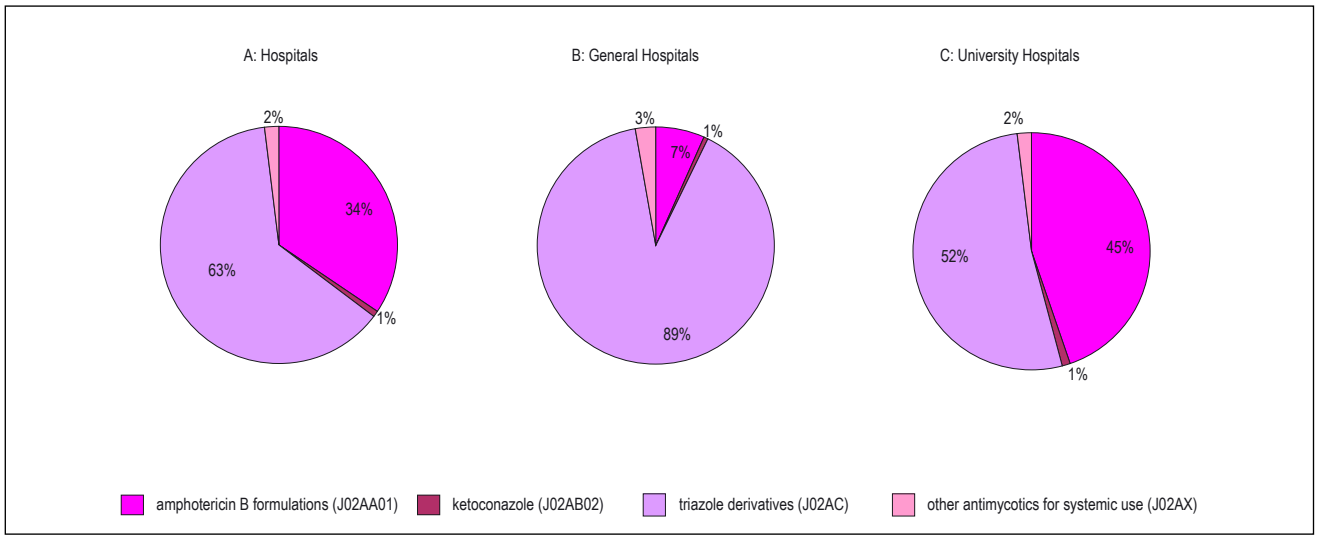


Figure 13. Distribution in 2007 of the use of antimycotics in all hospitals (A), General Hospitals (B) and University Hospitals (C).

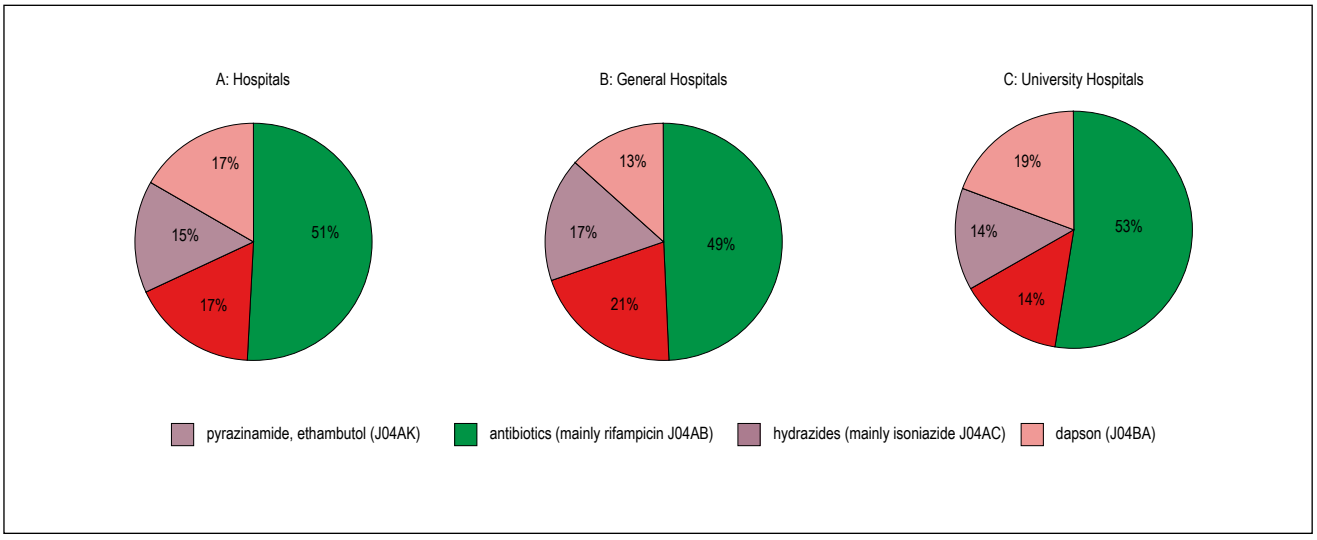


Figure 14. Distribution in 2007 of the use of antimycobacterial drugs in all hospitals (A), General Hospitals (B) and University Hospitals (C).

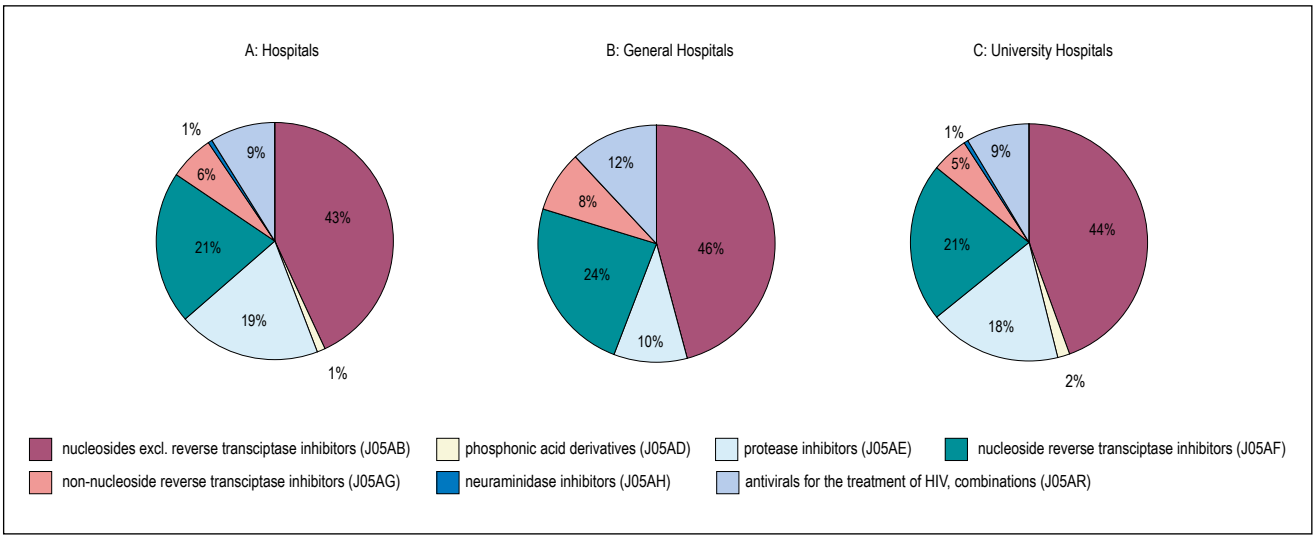


Figure 15. Distribution in 2007 of the use of antiviral drugs in all hospitals (A), General Hospitals (B) and University Hospitals (C).

Download from SWAB.nl | 2026-11-12 14:20

Table 6. Use of antimycotics for systemic use (J02) in hospitals (DDD/100 patient-days), 2006-2007 (Source: SWAB).

		2006			2007		
ATC groupa	Therapeutic group	Totaal2006 (n=44)	General hospitals (n=39)	University hospitals (n=5)	Totaal2006 (n=38)	General hospitals (n=31)	University hospitals (n=7)
J02AA01	Antibiotics (Amfotericin B)	0.97	0.12	5.61	1.50	0.12	4.44
J02AB02	Imidazole derivatives (Ketoconazol)	0.03	0.03	0.03	0.04	0.01	0.12
J02AC	Triazole derivatives	2.16	1.38	6.41	2.74	1.59	5.18
J02AX01	Flucytocin	0.01	0.01	0.02	0.01	0.00	0.01
J02AX04	Caspofungin	0.04	0.02	0.16	0.09	0.04	0.18
J02	Antimycotics for systemic use (total)	3.21	1.56	12.23	4.38	1.76	9.93

a) From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 7. Use of antimycobacterials for systemic use (J04) in hospitals (DDD/100 patient-days), 2007 (Source: SWAB).

ATC groupa	Therapeutic group	Totaal2007 (n=37)	General hospitals (n=30)	University hospitals (n=7)
J04AB	Anitbiotics (rifampicin)	0.83	0.52	1.44
J04AC	Hydrazides (isoniazide)	0.28	0.22	0.39
J04AK	Other drugs for the treatment of tuberculosis (pyrazinamide, ethambutol)	0.25	0.18	0.38
J04BA	Drugs for the treatment of lepra (dapson)	0.27	0.14	0.53
J04	Antimycobacterials for systemic use (total)	1.63	1.06	2.74

a) From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 8. Use of antivirals for systemic use (J05) in hospitals (DDD/100 patient-days), 2007 (Source: SWAB).

ATC groupa	Therapeutic group	Totaal2007 (n=36)	General hospitals (n=29)	University hospitals (n=7)
J05AB	Nucleosides and nucleotides excl reverse transcriptase inhibitors	0.78	0.27	1.72
J05AD	Phosphonic acid derivatives	0.02	0	0.06
J05AE	Protease inhibitors (PI's)	0.28	0.06	0.70
J05AF	Nucleosides and nucleotides reverse transcriptase inhibitors (NRTI's)	0.35	0.14	0.83
J05AG	Non-nucleosides reverse transcriptase inhibitors (NNRTI's)	0.10	0.05	0.20
J05AH	Neuraminidase inhibitors	0.01	0	0.02
J05AR	Anitvirals for the treatment of HIV, combinations	0.15	0.07	0.33
J05	Antivirals for systemic use (total)	1.81	0.59	3.86

a) From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

From 1999 to 2006 co-amoxiclav, the most commonly used penicillin showed an increase in both units of measurement (figures 7A and B). In 2007, a decrease in the use of most penicillins was found.
Cephalosporins represented 14% of the total of in-hospital antibiotic use (figure 6). The use of first and third generation cephalosporins was increasing steadily, while the use of second generation cephaloporins seemed to stabilise (figures 8A and B).
Apparently, the use of macrolides is also stabilising. Within the group, some shifting use of the individual macrolides was observed. The use of erythromycin and clarithromycine was decreasing over the past years, whereas the use of azithromycine was rapidly increasing. However, azithromycin use was still used the lowest of all macrolides (figures 9A and B).
The use of all aminoglycosides remained more or les constant from 1999 to in 2007. Gentamicin was the most commonly used aminoglycoside (figures 10A and B).
Overall, the use of ciprofloxacin was increasing,

Download from SWAB.nl | 2026-11-12 14:20

expressed in both units of measurement, while the use of the other quinolones remained relatively low (figures 11A and B).
Vancomycin use was increasing markedly in both units of measurement and had more than doubled since 1999 when expressed in DDD/100 patient-days. The use of teicoplanin remained low (figures 12A and B).

Hospital use of systemic antimycotics

Total use of antimycotics for systemic use was 4.38 DDD per 100 patient-days (table 6). In university hospitals, the use of systemic antimycotics was almost six times higher compared to that in general hospitals. This is mainly the result of use of antibiotics (amfotericin B) and triazole derivatives of which fluconazol is used the most (figures 13A, B and C). This is consistent with the results in 2006.

Hospital use of systemic antimycobacterials

This year the use of anti-infectives for lepra and tuberculosis (J04) is also reported. The total use of antimycobacterials for systemic use was 1.32 DDD/100 patient-days (table 7). The distribution of the different groups of drugs was more or less similar in university hospitals and general hospitals (table 7 and figures 14A, B and C). Rifampicin represented approximately 50% of total use.

Hospital use of systemic antivirals

The use of antivirals in 2007 was on average 1.81 DDD/100 patient-days. University hospitals used almost seven times as much as general hospitals (4.09 vs. 0.56 DDD/100 patient-days) (table 8). Use of nucleosides and nucleotides, excluding reverse transcriptase inhibitors, was predominant in both hospitals (figures 15B & C). In University hospitals, this is mainly due to the use of valacyclovir and valganciclovir. In general hospitals acyclovir and valacyclovir are the most common representatives, while valganciclovir use is very low (data not shown).

Discussion

The unit in which antibiotic usage is expressed matters (7). This is important when hospital resource indicators change over a study period. In relation to antibiotic resistance development, the measure of antibiotic use should be a reflection of the antibiotic selection pressure exerted. At the population level the selection pressure is thought to depend on the volume of antibiotics used in a particular geographical area, the number of individuals exposed and the proportion of the population treated with antibiotics (8). The denominator should thus preferably include information on all these factors. However, there is a lack of studies to determine the correlation between different measures of antibiotic use and the level of antibiotic resistance.
Since NethMap 2004, data on antibiotic use in Dutch hospitals have been expressed in DDD per 100 patient-days and in DDD per 100 admissions.
We have distinguished four main categories with regard to the observed trends in antibiotic use in hospitals. An increase in both the number of DDD per 100 patient-days and the number per 100 admissions (category 1) is worrisome and that no increase in either unit (categories 3, 4) is not worrisome with regards to resistance development. The trends in category 2 are less easy to interpret.
When a constant use per patient (category 2) is seen, and this is combined with an increase in the number of admissions, this is indicative for an increase of the selection pressure exerted by antibiotics in hospitals over the years.
An intensification of antibiotic therapy per 100 patient-days, however, may in part be due to an increase in the number of admitted patients, and possibly a shortening of the duration of antibiotic treatment. Such shortening of the duration of therapy may lead to less selection of resistant micro-organisms (9).
In 2007, the total antibiotic use decreased referred to the year before when expressed in DDD/100 patient-days. However, there was still an increase of 17% observed over the 5-year period 2003-2007. The average patient however, did not use more antibiotics.
Despite the stable use per patient, the average hospital environment is exposed to 17% more antibiotics in 2007 compared to 2003. This higher ecological pressure may result in the selection of resistant strains in individual patients.
The consumption of ciprofloxacin and vancomycin has significantly increased since 1999. This might be due either to an increased focus on staphylococcal infections or an increased incidence of serious staphylococcal infections in the community and in health care settings. An increase in the incidence of gram-negative resistant micro-organisms might explain the increase in ciprofloxacin use.
In university hospitals, the use of systemic antimycotics is almost six times higher compared to general

Download from SWAB.nl | 2026-11-12 14:20

hospitals. This is explained by the high concentration of haematology and oncology-patients in university hospitals.
Although university hospitals use twice as much antimycobacterials, the distribution of the different groups is rather similar. The treatment of tuberculosis in the Netherlands consists of a combination of a limited amount of primary antimycobacterials. Therefore, there is not much room for variation (10).
Rifampicin is, besides its use for tuberculosis, also used as an adjuvant in certain infections with gram positive staphylococci (*N. meningitidis, H. influenzae*).
The use of dapson is explained by its place in the prophylaxis and treatment of Pneumocystis carinii infections and toxoplasmic encephalitis in patients with AIDS.
The largest group of antivirals used are the nucleosides (excl. reverse transcriptase inhibitors) like (val)acyclovir and (val)ganciclovir. The difference in use between university hospitals and general hospitals can in part be explained by its use in prophylaxis and treatment of cytomegalovirus in transplant patients, who are usually treated in university hospitals.
In The Netherlands, all university hospitals and a few general hospitals are specialised in the treatment of HIV patients. These general hospitals use significantly more antivirals than the others (data not shown).
The performance of point prevalence surveys is a useful tool to determine the appropriateness of antibiotic therapy and give insight into the demographics, infections and antibiotics used within specific hospital populations (11).

References

1. MARAN-2005 – Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in The Netherlands In 2005.
2. Akkerman AE, Kuyvenhoven MM, Verheij TJM, van Dijk L. Antibiotics in Dutch general practice; nationwide electronic GP database and national reimbursement rates. Pharmacoepidemiol Drug Saf 2007 oct 11 [epub ahead of print] DOI: 10.1002/pds.1501
3. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005; 365: 579-87
4. Kuyvenhoven MM, Balen FAM van, Verheij TJM. Out-patient antibiotic prescriptions from 1992 till 2001 in the Netherlands. J Antimicrob Chemother 2003; 52, 675-8
5. Wise R. The relentless rise of resistance. J Antimicrob Chemother 2004; 54: 306-10
6. van Haaren KAM, Visser HS, van Vliet S, Timmermans AE, Yadava R et al. NHG standaard Urineweginfecties (tweede herziening). Huisarts Wet 2005; 48: 341-52
7. Filius PMG, Liem TBY, van der Linden PD, Janknegt R, Natsch S, Vulto AG and HA Verbrugh. An additional measure for quantifying antibiotic use in hospitals. J Antimicrob Chemother. 2005;55:805-8.
8. Levy SB. Antibiotic resistance: Consequences of inaction. Clinical Infectious Diseases 2001;33, Suppl.3, S124-9.
9. Schrag SJ, Pena C, Fernandez J. et al. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. JAMA 2001;286:49-56.
10. Richtlijn medicamenteuze behandeling van tuberculose 2005. Nederlandse vereniging voor artsen voor longziekten en tuberculose. Van Zuiden Communications BV. ISBN 90-8523-102-7.
11. Willemsen I, Groenhuijzen A, Bogaers D, Stuurman A, van Keulen P, Kluytmans J. Appropriateness of antimicrobial therapy measured by repeated prevalence surveys. Antimicrob Agents Chemother. 2007;51(3):864-7.

Download from SWAB.nl | 2026-11-12 14:20

4. Resistance among common Pathogens

Use of EUCAST susceptibility criteria in NETHMAP

In 1999 the SWAB Resistance Surveillance Standard was published. This guideline was made by the SWAB Working Group on Antimicrobial Resistance and contains criteria for indicator-organisms, indicator-antibiotics, methods and breakpoints for qualitative and quantitative susceptibility testing. The breakpoints chosen were those defined by the CLSI (Clinical Laboratory Standards Institute, USA; formerly NCCLS) because of several reasons of which most important were the possibility to compare our data with other international surveillance data and to be able to publish the results in important international journals. From the beginning some problems were identified when using these breakpoints for organisms associated with respiratory and tissue infections, because of the height of the breakpoint for resistance for some organisms, which looked unrealistic. Therefore lower breakpoints for respiratory pathogens were used in former issues of NethMap, based on own criteria, often those of the Dutch CRG (Commissie Richtlijnen Gevoeligheidsbepalingen). Non-withstanding, data obtained from laboratories as S, I or R - the interpretation of MIC or zone diameters being done locally – were the results of unknown breakpoints locally used. Consequently, resistance rates obtained from MIC data could be well compared over time and with other countries that did use CLSI breakpoints, but data obtained as S, I, or R were less illuminating.
To harmonize breakpoints in Europe, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) instigated a working party, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in 1997, which was restructured in 2001, chaired by Professor Gunnar Kahlmeter. In 2008, harmonized breakpoints for all antimicrobials commonly used became available and are now being applied or starting to being used in many countries in Europe. Meanwhile, EUCAST is now funded by the European Centre for Disease Prevention and Control (ECDC) and this organization has adopted EUCAST guidelines. In addition, by a formal arrangement with the European Medicines Agency, EUCAST sets breakpoints for new antimicrobials as part of the regulatory process, which are now part of the Summary of Product Characteristics (SPC) in Europe. Because of this the decision was made by the SWAB to replace interpretative criteria from CLSI by EUCAST. There are, however, some consequences of this decision. The resistance rates recorded by EUCAST criteria are seemingly higher in some cases because many EUCAST breakpoints for resistance are lower than CLSI breakpoints. Therefore, the data based on MIC data (those from the community and selected hospital departments) have been reinterpreted so that trends could be followed without interruption; this implies that resistance rates presented in NethMap 2009 are not comparable with those presented in former issues of NethMap. Further most longitudinal data from selected hospital departments are evaluated by use of both EUCAST criteria and CLSI criteria to show the differences. This was not possible for the data where only qualitative, categorical data were available. It is expected that most Dutch laboratories will have converted to EUCAST criteria within one or two years. This will significantly facilitate interpretation of resistance data both within The Netherlands as well as with surrounding countries.

Surveillance of Antimicrobial Resistance in the Community

The studies on resistance level in the community focus on three different goals: (1) estimation of resistance in the indigenous flora of healthy persons in various circumstances and of various ages, giving information about the basic level of resistance in human reservoirs and (2) estimation of resistance in patients visiting their general practitioner (GP), and (3) estimation of resistance in special pathogens like meningococci, gonococci and mycobacteria.
Several longitudinal multicentre studies within the national project Surveillance of Extramural Resistance in The Netherlands (SERIN) were carried out or are ongoing in various parts of The Netherlands in cooperation with the Department for Medical Microbiology, University Hospital Maastricht, The Netherlands Institute for Health Services research (NIVEL) and the regional Institutes for Public Health Services (GGDs).
Resistance data were obtained for *Staphylococus aureus* as part of the indigenous flora of healthy persons and of residents of nursing homes. Another surveillance project was carried out to determine the carrier state and level of resistance of *Streptococcus pneumoniae* in healthy children and adults.
In 2006, RIVM started a surveillance of resistance of *Neisseria gonorrhoeae* among patients from outpatient-STD clinics, the so-called “GRAS project”.
Since 1993, The Netherlands Reference Laboratory for Bacterial Meningitis determines the resistance level of *Neisseria meningitidis* from patients admitted to the hospital for meningococcal disease.
The first isolate of *Mycobacterium tuberculosis* of each patient with tuberculosis in The Netherlands is routinely sent to the RIVM for susceptibility testing and confirmation of identification. Results of all these studies are presented here.

Download from SWAB.nl | 2026-11-12 14:20

Staphylococus aureus

The prevalence of antibiotic resistance among *S. aureus* as part of the indigenous flora of residents of nursing homes was determined to get insight in the carrier state and the basic level of resistance in this reservoir in the community. This study was performed in 2007 and 2008. The carrier state in these nursing homes was compared with the carrier state in healthy volunteers. The resistance level in nursing home residents was compared with that in healthy individuals and in patients from Unselected Hospital Departments in 2008, included in the ISIS-AR program (see Materials and Methods for details).

Nasal swabs were taken after informed consent was obtained from residents in six nursing homes in Maastricht and Utrecht, cities in the Southern and middle part of The Netherlands, respectively. Two hundred and sixty residents having somatic disabilities without infections were screened and 105 of them carried *S. aureus* (40%). A total of 115 strains were isolated.

A random sample of 4000 healthy individuals between 18 and 75 years of age was taken from the municipal administration in Heerlen, a city in the Southern part of The Netherlands (see Materials and Methods for details). A total of 2369 nasal swabs were obtained and *S. aureus* was isolated in 654 samples (28%), which is significantly lower than the carrier rate in nursing home residents ($p< 0.01$).

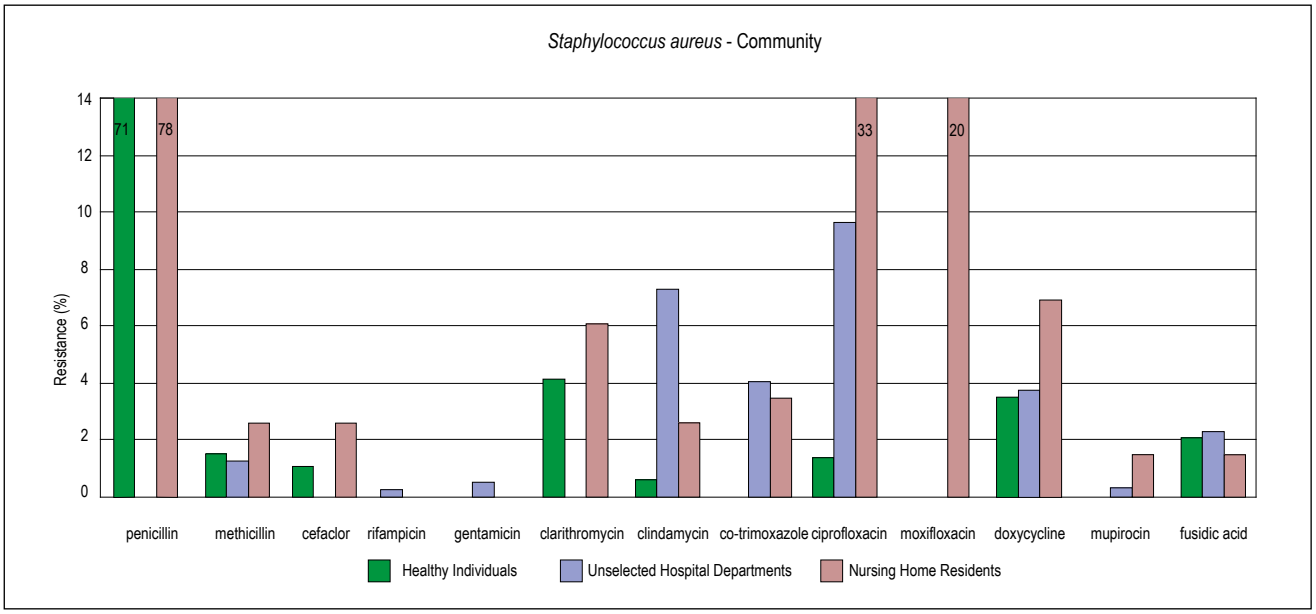
Penicillin resistance was found in 78% of the strains from nursing home residents compared with 72% in healthy individuals. The distribution of MICs for both populations (not shown) was bimodal with one population (27%) having MICs <0.06 mg/l and a second population (73%) with MICs over a large area (0.25-16 mg/l) with MIC_{90} 8 mg/l.

Methicillin resistance was 2.6% in nursing home residents, 1.5% in healthy individuals and 1.3% in patients from Unselected Hospital Departments. Two strains from nursing home residents (0.8%) and two of healthy individuals harboured the mecA gene and were classified as MRSA. So, 0.3% of the *S. aureus* carriers of healthy individuals had an MRSA, which is 0.1% of the total healthy population in The Netherlands.

Imipenem and meropenem resistance was not observed in nursing home residents, in contrast to healthy individuals (0.5%) and patients in Unselected Hospital Departments, where a small percentage of strains appeared to be resistant (0.6-0.9%). Cefaclor and cefuroxime resistance was 3% in nursing home residents compared to 1.5% in healthy individuals. The MIC distributions of cefaclor (figure 2) and cefuroxime for strains from nursing home residents were bimodal with a large subpopulation in the range with MICs 0.5-4 mg/l and a small subpopulation with MICs > 8 mg/l. The resistant subpopulation was not observed in healthy individuals. Clarithromycin resistance was observed in 6% of strains from nursing home residents, which is somewhat higher than the level in healthy individuals (4%), but clindamycin resistance was significantly higher in patients from Unselected Hospital Departments (7%) compared to that nursing homes (3%) and in healthy individuals (1%). The MIC distributions for clarithromycin were bimodal with a large subpopulation in the range from < 0.12-1 mg/l and a small subpopulation with MIC > 8 mg/l. The median was 0.5 mg/l for healthy individuals and 1 mg/l for nursing home residents.

No difference in resistance level for co-trimoxazole (4%) was observed between the nursing homes and the Unselected Hospital Departments; no resistance was

Figure 1. Resistance to antibiotics among *Staphylococcus aureus* from healthy individuals, patients from Unselected Hospital Departments and nursing home residents in 2007/2008.

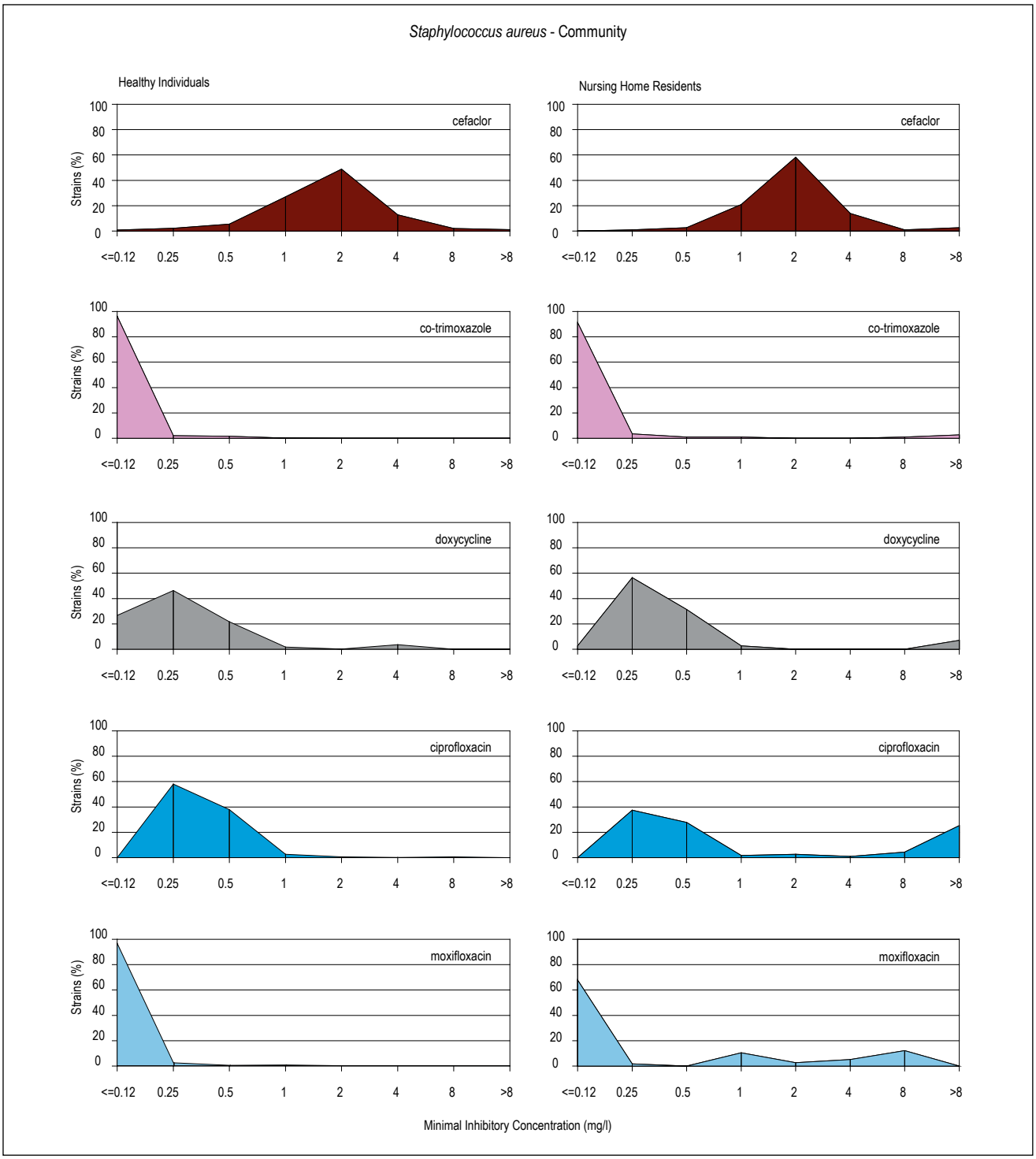


Download from SWAB.nl | 2026-11-12 14:20

observed in healthy individuals. The MIC distributions of strains from nursing home residents were bimodal with a small subpopulation with MICs > 8 mg/l. This subpopulation was not observed for strains from healthy individuals (figure 2).
Doxycycline resistance in nursing home residents was 7% compared to 4% in patients from Unselected Hospital Departments and healthy individuals (p< 0.01).

The MIC distributions for strains from nursing home residents and healthy individuals were bimodal (figure 2). The susceptible subpopulation in strains from healthy individuals had MICs ranging from 0.06-0.5 mg/l, that in strains from nursing home residents ranged from 0.25-0.5 mg/l, whereas the resistant population in nursing homes (MIC > 8 mg/l) was larger (figure 2).
Overall ciprofloxacin resistance was recorded in 33%

Figure 2. MIC distributions of antibiotics for *Staphylococcus aureus* from healthy individuals and nursing home residents.

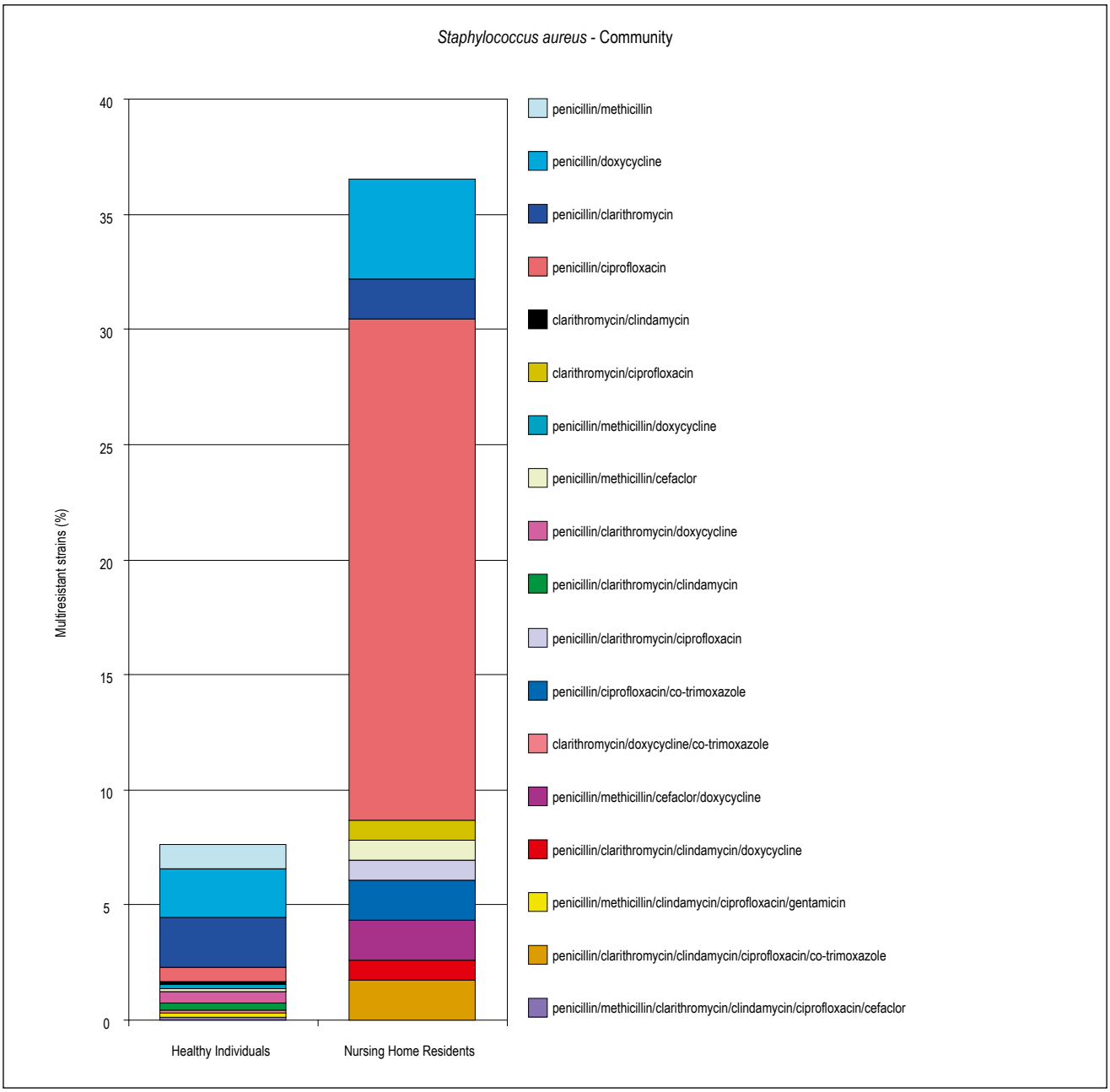


Download from SWAB.nl | 2026-11-12 14:20

of the strains from nursing home residents, which is significantly higher than in healthy individuals (1%) and patients from Unselected Hospital Departments (10%, $p<0.01$) (figure 1). The differences in resistance levels between the six nursing homes were not significant. The MIC distribution of strains from nursing home residents was bimodal with one susceptible population (MIC <2 mg/l) and one resistant subpopulation (MIC > 8 mg/l), that of healthy individuals was unimodal with some strains with MICs 2-8 mg/l (figure 2). Moxifloxacin resistance in nursing homes was high as well (20%); moxifloxacin resistance was not found in healthy individuals. The MIC distributions for moxifloxacin showed also a bimodal shape for strains from nursing home residents and a unimodal one for healthy individuals. In general the MICs for moxifloxacin were 4-fold lower than for ciprofloxacin with MIC_{90} 0.12 mg/l. These resistance rates may reflect selection by frequent use of quinolones for various indications in nursing homes (figure 2).

All isolates from nursing home residents were susceptible to vancomycin, teicoplanin, gentamicin, imipenem, meropenem and rifampicin. The resistance level to mupirocin and fusidic acid was 2%, the latter was also found in healthy individuals and patients from Unselected Hospital Departments.

Figure 3. Multiresistance among *Staphylococcus aureus* from healthy individuals and nursing home residents in 2007/2008.



Download from SWAB.nl | 2026-11-12 14:20

Multiresistance of *Staphylococus aureus* in the community and nursing homes

Combined resistance to two or more antibiotics for systemic use was found in 6% of the strains from healthy individuals and in 29% of the strains from nursing home residents (figure 3). The combinations penicillin/doxycycline and penicillin/clarithromycin predominated in healthy individuals, the combination penicillin/ciprofloxacin predominated in strains from nursing home residents. Multiresistance (resistance to three or more antibiotics of different classes) was demonstrated in 1.5% of the strains from healthy individuals. When extrapolated to the community as a whole: 0.35% of the healthy Dutch population is carrier of multiresistant *S. aureus*. Multiresistance was demonstrated in 8% of the strains from nursing home residents: 3.5% of the strains were resistant to three antibiotic classes, 4.5% for four or more antibiotics. This high frequency of multiresistance in residents of nursing homes is a matter of concern. It may reflect selection by frequent use of antibiotics in a closed community and poses a serious problem for the treatment of infections in patients of nursing homes.

Streptococcus pneumoniae

The carrier state and prevalence of antibiotic resistance among *S. pneumoniae* as part of the indigenous throat flora of healthy persons was compared with the carrier state and resistance of this micro-organism in patients with complaints of a lower respiratory tract infection visiting their general practitioner (GP).

Carrier state and antibiotic resistance level of *Streptococcus pneumoniae* in healthy individuals

Three populations were studied: (I) children at 0-4 years of age from day care centres (infants, N=620), (II) children at nine years of age (young children, N=698) and (III) adults at the age of 60 years and more (N=593). Three subpopulations with respect to the pneumococcal vaccination status within the infants were identified: (1) infants vaccinated with pneumococcal conjugate vaccine, (2) incompletely vaccinated infants and (3) non-

Figure 4. Resistance to antibiotics among *Streptococcus pneumoniae* from healthy infants (0-4 years of age) in 2007/2008.

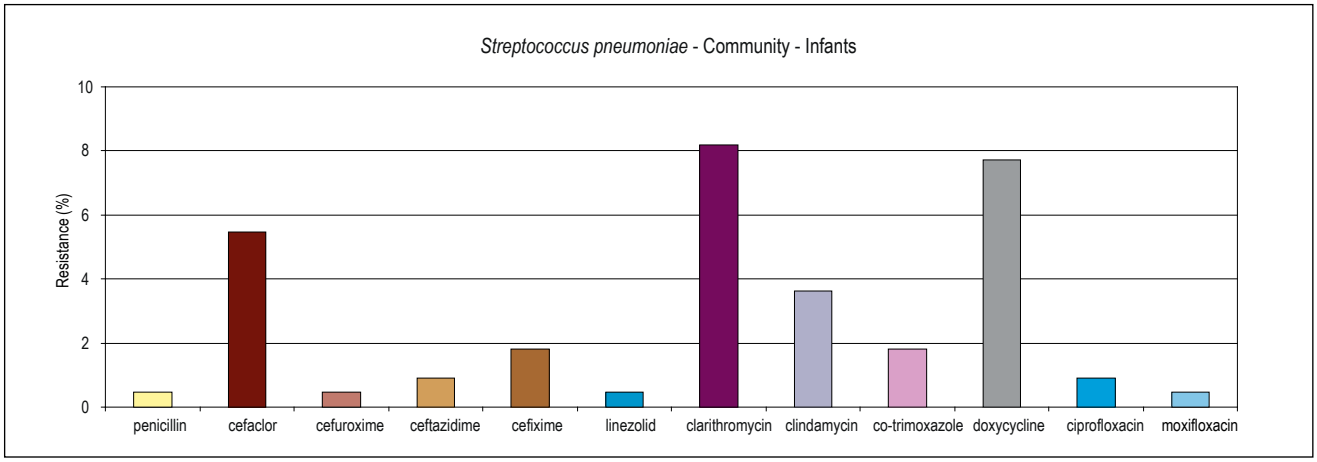
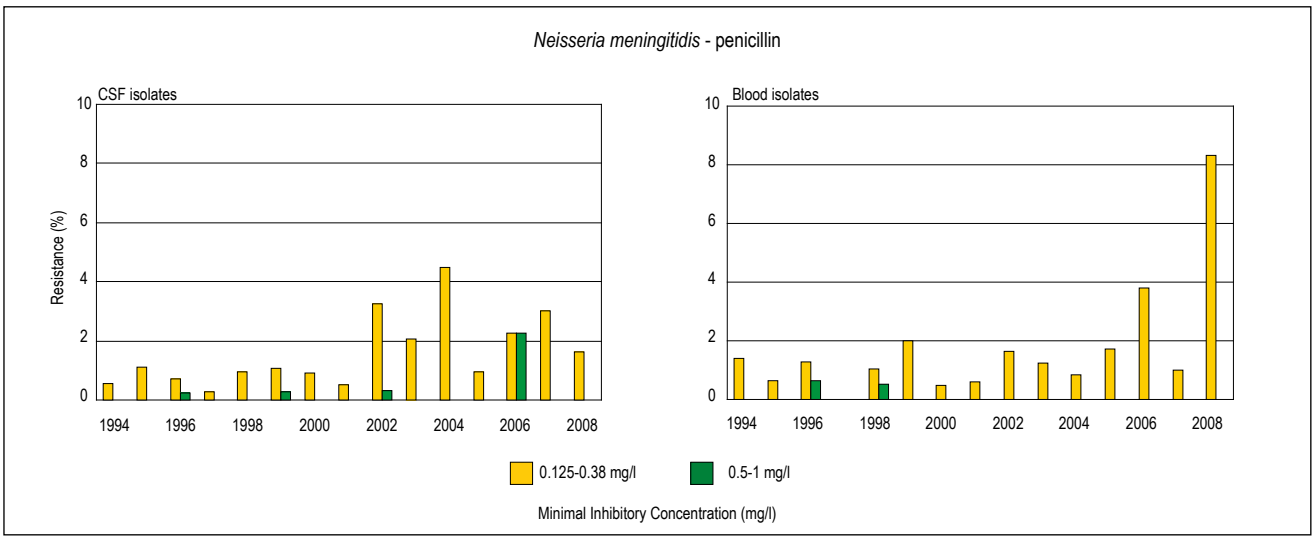


Figure 5. Trends in penicillin resistance among clinical strains of *Neisseria meningitidis*.



Download from SWAB.nl | 2026-11-12 14:20

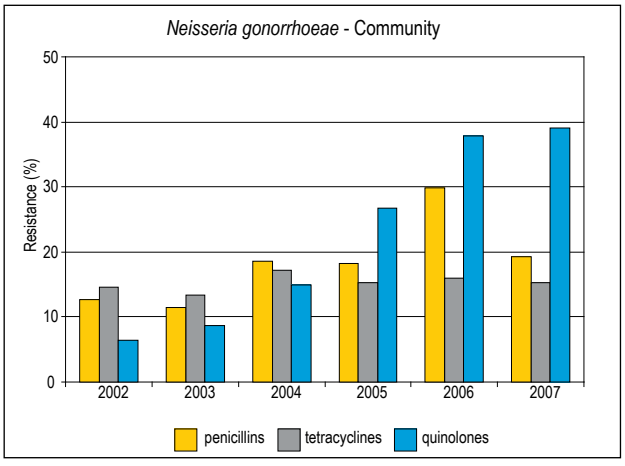
vaccinated infants. Throat swabs from young children and adults and deep nose swabs from infants were taken after informed consent was obtained and then cultured for *S. pneumoniae*. A total of 221 strains were isolated from infants (overall carrier rate 36%). The carrier rate of *S. pneumoniae* varied with the vaccination status against *S. pneumoniae*: it was 38% in non-vaccinated infants, 31% in incompletely vaccinated infants and 47% in vaccinated infants. The latter strains were defined as non-vaccine strains. The carrier rate of *S. pneumoniae* in young children was much lower (4%). This was not surprising knowing that the pneumococcal carrier rate of infants in day care centres is always much higher than that in other children because of intensive contacts between the infants in a semi-closed environment. It is possible that some carriers in young children were missed because of the technique of sampling used (throat swabs instead of deep nose swabs). The carrier rate in adults was 2%. The susceptibility patterns of the isolates from the three subpopulations in infants did not differ from each other. One of 221 strains (0.5%) was resistant to penicillin (figure 4), five strains were moderately susceptible to penicillin (MIC 0.12-0.25 mg/l). No penicillin resistance was found young children and in healthy adults, although the number of strains in these groups were low (N = 29 and N= 11, respectively). Amoxicillin resistance was not found in any of the groups studied.
Cefaclor resistance was 5.5% in infants and it was also often found in young children (8 of 29 strains) and in adults (5 of 11 strains). Resistance to the other cephalosporins tested was less than 1% in infants and it was sporadically found in the other study groups. Resistance to clarithromycin was 8% in infants and 13% in young children and it was only found once in adults. Co-trimoxazole resistance was 1.8% in infants compared with 3% in young children. Striking was the finding of 12 out of 29 strains from young children being resistant to ciprofloxacin (MIC 4-8 mg/l) compared with 1% in infants and 0% in adults. We have no explanation for this finding since the young children came from various areas in the Southern part of the country and ciprofloxacin is not advised in children at all. Isolates of all study groups were susceptible to levofloxacin, moxifloxacin, imipenem, meropenem, rifampicin, teicoplanin and vancomycin.

Carrier state and antibiotic resistance level of *Streptococcus pneumoniae* in patients with complaints of a lower respiratory tract infection
Thirty general practitioners (GP) from across The Netherlands participated in the study. A total of 451 patients visiting their GP with complaints of a lower respiratory tract infection were included in the study. Seventeen strains of pneumococci were isolated, reflecting a carrier rate of 3.8%, which is significantly higher than that found in healthy adults (2%, $p< 0.05$). Two strains were moderately susceptible to penicillin (MIC 0.25 mg/l). No resistance to any of the other antibiotics tested was found.

Neisseria meningitidis
From 1994-2008, a total of 4514 strains from cerebrospinal fluid and 2637 strains from blood were included in the surveillance project of The Netherlands Reference Laboratory for Bacterial Meningitis of the Academic Medical Centre, Amsterdam. Strains moderately susceptible to penicillin (MIC 0.125-0.38 mg/l) occurred in less than 1% of the strains before 2002. Thereafter, 2-4% of strains from CSF appeared moderately susceptible. The same pattern was observed in strains from blood until 2007, but in 2008 seven isolates (8%) appeared moderately susceptible (figure 5). Three of these seven strains belonged to serogroup B, the other strains to the serogroups C (one of five isolates), W135 (two of three strains) and Y (one of seven isolates), respectively. Penicillin resistance (MIC >0.5 mg/l) was occasionally found in strains both from CSF and blood (figure 5). All strains isolated in 2007 and 2008 were susceptible to ceftriaxone and rifampicin.

Neisseria gonorrhoeae
In 1999, the nationwide surveillance of antibiotic resistance in gonococci was discontinued and since then insight in the susceptibility patterns of gonococci has been limited. Concern over the increasing resistance to quinolones resulted in the introduction of an annual questionnaire administered by the RIVM on resistance of gonococci from 2002 onwards. Complete data on the number of diagnoses and the results of antimicrobial susceptibility testing were provided by 22 of 39 microbiological laboratories for the period of 2002-2007. Overall penicillin resistance increased from 10% in 2002 to 30% in 2006 and decreased again to 19% in 2007 (figure 6). Doxycyline resistance remained stable around 15%. Ciprofloxacin resistance increased from 6% in 2002

Figure 6. Trends in antibiotic resistance among strains of *Neisseria gonorrhoeae* in The Netherlands, 2002-2007 (Source; RIVM questionnaire among microbiological laboratories).



Download from SWAB.nl | 2026-11-12 14:20

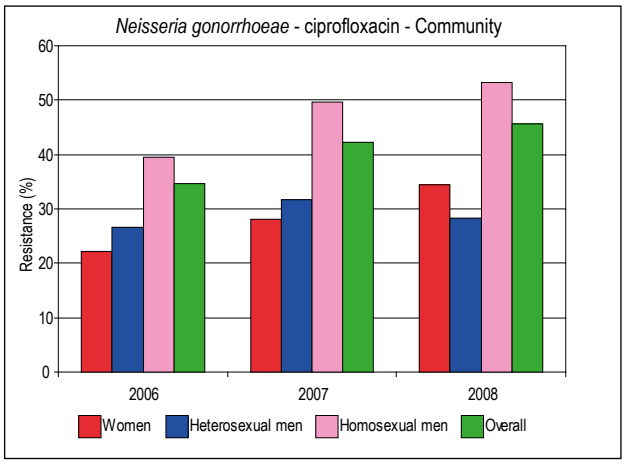


Figure 7. Trends in ciprofloxacin resistance among strains of *Neisseria gonorrhoeae* in The Netherlands, 2006-2008 in different study groups (GRAS project).

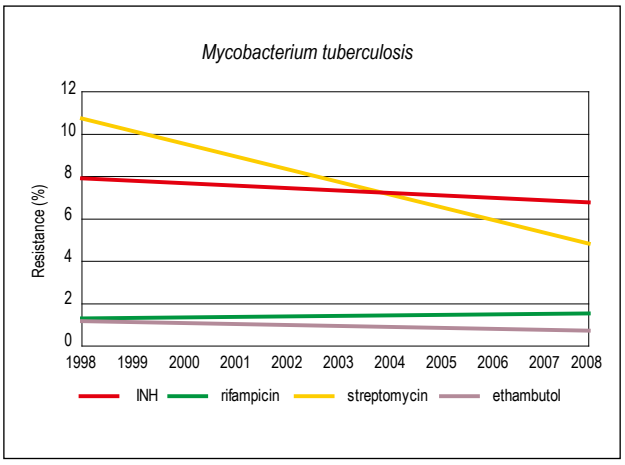
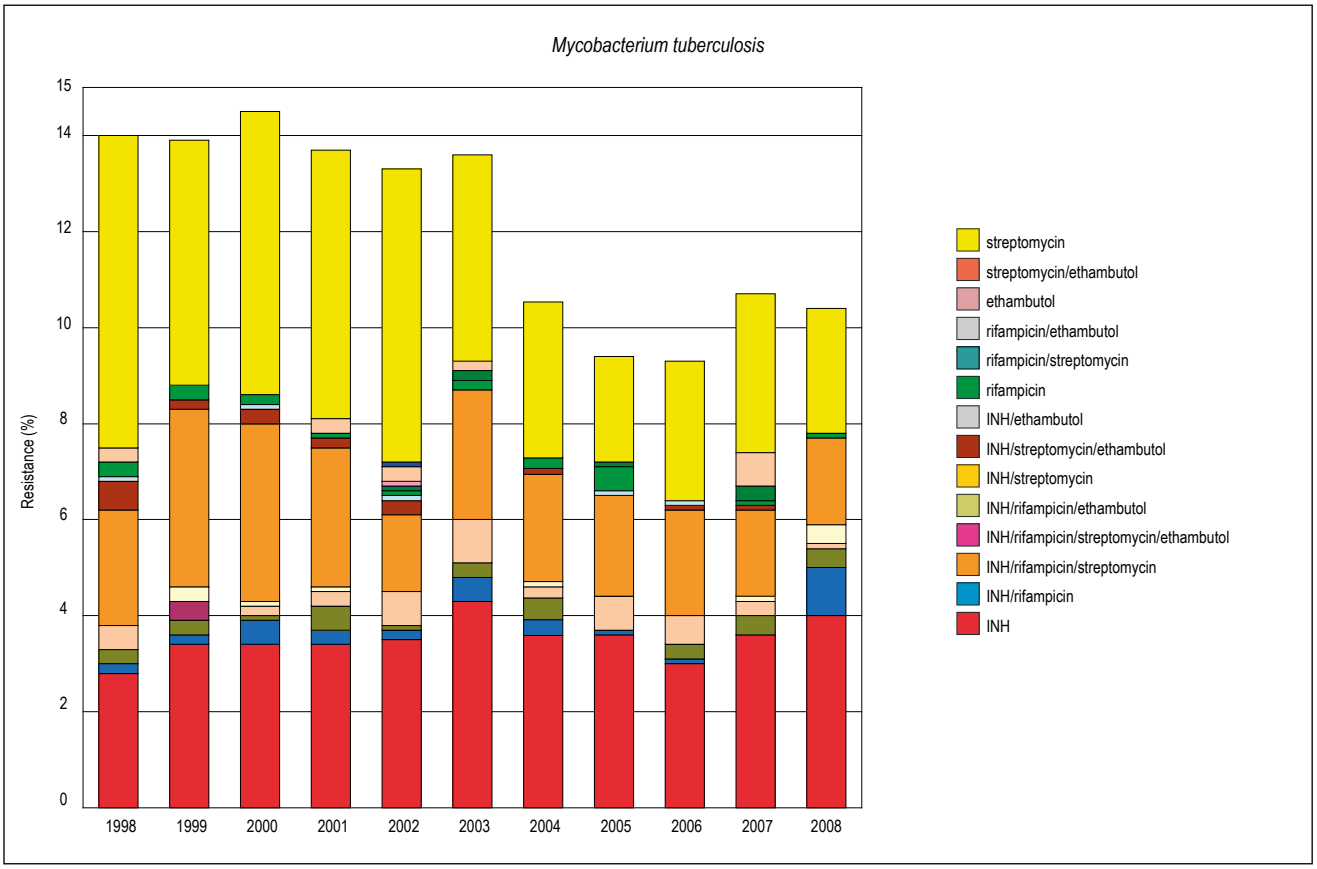


Figure 8. Trends in antibiotic resistance among *Mycobacterium tuberculosis.*

to 39% in 2007. Resistance to cefotaxime or ceftriaxone was not observed. Taking a maximum of 5% resistance acceptable for empiric therapy only cefotaxime and ceftriaxone can continue to be used in this setting.
In addition to this annual questionnaire, a Gonococcal Resistance to Antimicrobials Surveillance (GRAS) project has been implemented in The Netherlands in 2006. This surveillance consists of systematically collected data on gonorrhoea and standardised, quantitative measurement of resistance patterns by using E-test, linked with epidemiological data. Isolates with unusual resistance patterns were forwarded to the RIVM for confirmation. STI clinics and associated laboratories that identify the majority of STI in high risk populations

Figure 9. Trends in combined antibiotic resistance among *Mycobacterium tuberculosis.*



Download from SWAB.nl | 2026-11-12 14:20

participated in this surveillance. In July 2006, the GRAS project was implemented in the first STI centre. Throughout 2006, 2007 and 2008 GRAS was further expanded and as of June 2008, most STI centres in The Netherlands, representing approximately 80% of the total population of clinic attendees participated in GRAS. Between July 2006 and July 2008, susceptibility testing for *N. gonorrhoeae* was performed for 1556 patients (174 in 2006, 939 in 2007 and 443 in the first half of 2008). In general, the resistance data collected by GRAS were similar to those reported by the microbiological laboratories in the RIVM questionnaire. Overall ciprofloxacin resistance rose further to 46% in 2008 ($p<0.05$). When looking at the resistance level in the subpopulations tested, it was shown ciprofloxacin resistance in heterosexual men was around 28% and did not increase between 2006 and 2008 (figure 7), whereas ciprofloxacin resistance increased further in 2008 in both women and homosexual men, the most in the latter group (53% in 2008, $p=0.05$). The prevalence of ciprofloxacin resistance in women from Eastern Europe was extremely high (89%).
The rapidly changing antibiotic resistance pattern of gonococci underlines the need for a continuous standardised surveillance of antimicrobial susceptibility to detect changes in resistance patters which might necessitate modification of treatment guidelines, to explore risk factors for infection with such strains and to understand high risk transmission patterns.

Mycobacterium tuberculosis
A total of 10,141 strains of *M. tuberculosis* complex were obtained during 1998-2008; the number of isolates is steadily decreasing since 1999. Then the number of first isolates was 1109, in 2008 it was 730.
INH resistance remained stable, 7.7% (figure 8), streptomycin resistance decreased from 10% in 1998 to 5% in 2005 and stayed at that level. Rifampicin resistance increased to 2% in 2008 and ethambutol resistance remained low, 0.5% in 2008. Combined resistance to more than one drug was observed in 3.7% of all isolates (figure 9), combined resistance to rifampicin and INH was recorded in 2% of the strains. Resistance to all four antimycobacterial drugs was 0.1% in 2008.

Surveillance of Antimicrobial Resistance in Hospitals

The overall prevalence of antibiotic resistance in hospitals was estimated by using qualitative resistance data generated in routine clinical care by regional public health laboratories and local laboratories and aggregated through the national Infectious Diseases Information System for Antibiotic Resistance (ISIS-AR), which is coordinated by the Centre for Infectious Disease Control Netherlands (CIb) at the National Institute for Public Health and the Environment (RIVM). These are designated resistance rates in "Unselected Hospital Departments". In 2007, ISIS-AR was revised by need of better definition and origin of strains, the more frequent use of automated systems for susceptibility testing and a more uniform use of international susceptibility criteria. This allowed us, e.g., to separate data collected from Outpatient Clinics and General Practice from clinical departments. Resistance rates in the Unselected Hospital Departments were compared with the resistance rates among strains isolated from selected departments in 14 large referral hospitals. The latter study is a longitudinal national study for Surveillance of Intramural Resistance in The Netherlands (SIRIN); the design of SIRIN differs significantly from ISIS-AR by generating quantitative susceptibility data, performed by the central laboratory of Medical Microbiology of the University Medical Centre Maastricht. The selected departments participating in SIRIN included the Intensive Care Units, being wards with high use of antibiotics and, consequently, high selective pressure favouring the emergence of resistance. Also included were the Urology Services and the Pulmonology Services, the latter two representing departments with frequent use of specific oral antibiotics. The quantitative data of all years were re-evaluated by use of EUCAST breakpoints. Since data in former NethMap issues were obtained by use of CLSI criteria for breakpoints, the results and figures in this issue of NethMap may differ from those presented in former issues. Results were analysed per species of common nosocomial pathogens and are presented in the accompanying figures. Resistance trends instead of detailed resistance percentages per year are given in most figures.

Escherichia coli
The overall prevalence of amoxicillin resistance in strains from Unselected Hospital Departments showed an increasing trend from 27% in 1998 to 44% in 2008 (figure 10). Amoxicillin resistance was higher in Intensive Care Units and showed considerable fluctuations between 2004 and 2007 (45-58%, not shown) but the overall trend was increasing from 41% in 1998 until 52% in 2007. The resistance in Urology Services fluctuated around 40% from the beginning, but showed a slow increase to 47% in 2007. The application of two breakpoints for resistance (EUCAST and CLSI) did not cause a significant difference in resistance percentages (figure 10). The distribution of MICs (figure 11) in Intensive Care Units showed two subpopulations: a susceptible one with a broad MIC range from 0.5-8 mg/l (peak at 2-4 mg/l) and a resistant one with MICs >32 mg/l. The resistant subpopulation was steadily growing during the years, whereas the peak of the susceptible one was flattening.
Co-amoxiclav resistance was at a low level, 4-5% in Unselected Hospital Departments until 2000, but overall a slight increase could be observed to 6% resistance in 2006 and 7% in 2008. This differs significantly from

Download from SWAB.nl | 2026-11-12 14:20

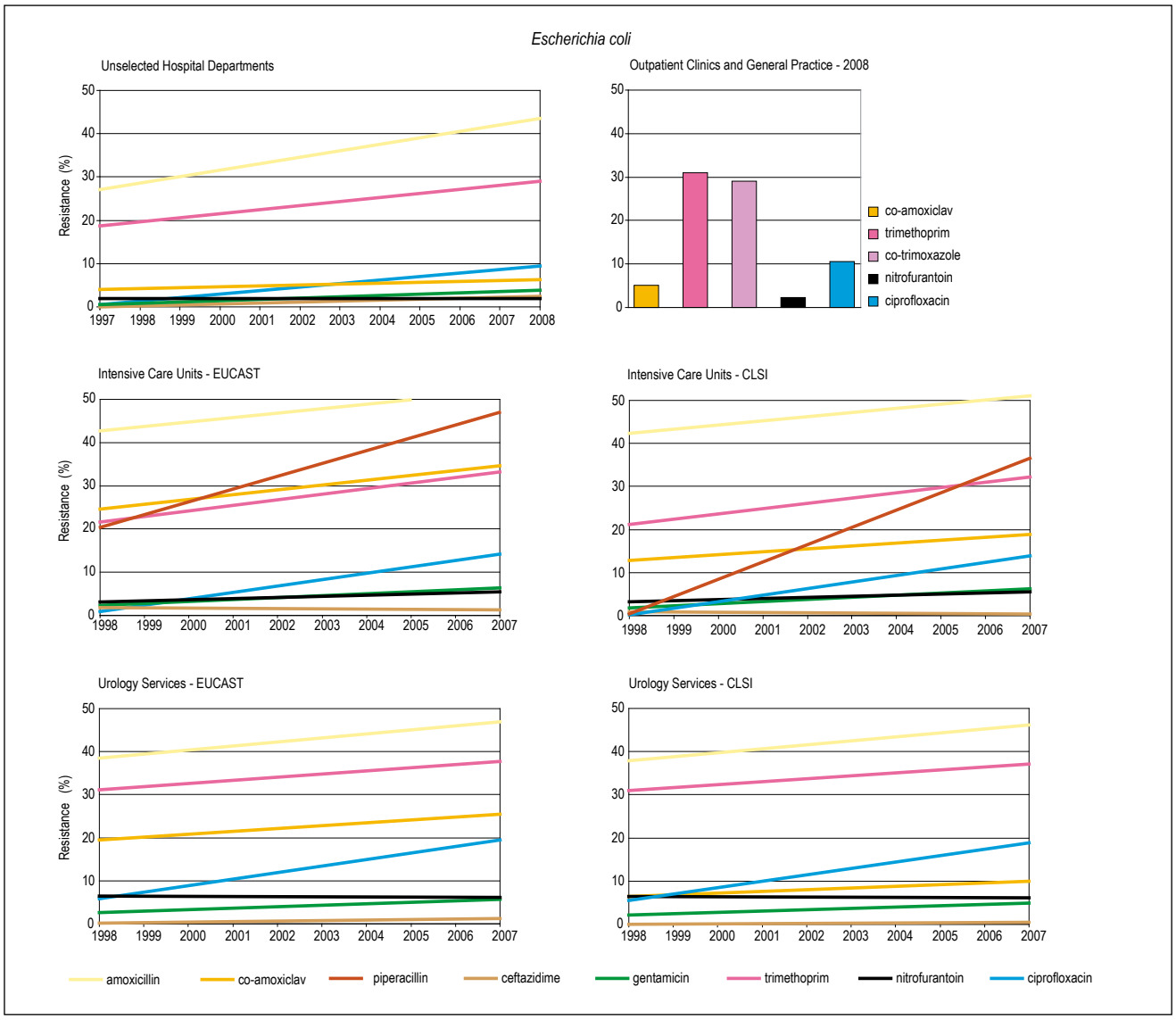


Figure 10. Trends in antibiotic resistance among clinical strains of *Escherichia coli* from Unselected Hospital Departments, Intensive Care Units and Urology Services and among urinary strains from Outpatient Clinics and General Practice. Trends in Intensive Care Units and Urology Services were calculated according to the breakpoints for resistance recommended by both EUCAST and CLSI.

the resistance rate among *E. coli* urinary isolates in Outpatient Clinics and General Practice which was 5% in 2008 (figure 10). The trend in the Urology Services was fluctuating but increasing from 19% in 1998 to 25% in 2007. Co-amoxiclav resistance was much higher in Intensive Care Units and the trend increased from 19% in 1998 to 25% in 2007. A clear influence of different breakpoints was observed for co-amoxiclav resistance rates: the resistance rate by use of the EUCAST breakpoint for resistance (MIC > 8 mg/l) was much higher than that obtained with the CLSI breakpoint for resistance (MIC > 16 mg/l) (figure 10). This can be easily understood when looking at the MIC distribution of co-amoxiclav: this was unimodal and showed a growing number of strains with MIC = 16 mg/l (figure 11), the breakpoint for resistance as recommended by EUCAST, but classified as intermediate by CLSI. The shape of the curve changed considerably over the years: until 2000 a real peak at 4 mg/l was observed, but this disappeared completely later. The existence of a growing intermediate population may predict upcoming resistance. Piperacillin resistance varied between the Intensive Care Units, some had high resistance rates (30%), others low (15%) until 2004, but from 2003 onwards the resistance level increased in all Intensive Care Units, resulting in an overall resistance rate of 47% in 2007. The application of two different breakpoints had effect on the outcome. The breakpoint for resistance recommended by EUCAST is MIC > 16 mg/l, whereas that of CLSI is MIC > 64 mg/l. Taking the latter breakpoint, the trend of resistance would have been from 0% in 1998 to 36% in 2007 (figure 10). The MIC distribution of piperacillin (figure 11) was bimodal, but showed an interesting shift since 2000. Two subpopulations were recorded in 1998: one

Download from SWAB.nl | 2026-11-12 14:20

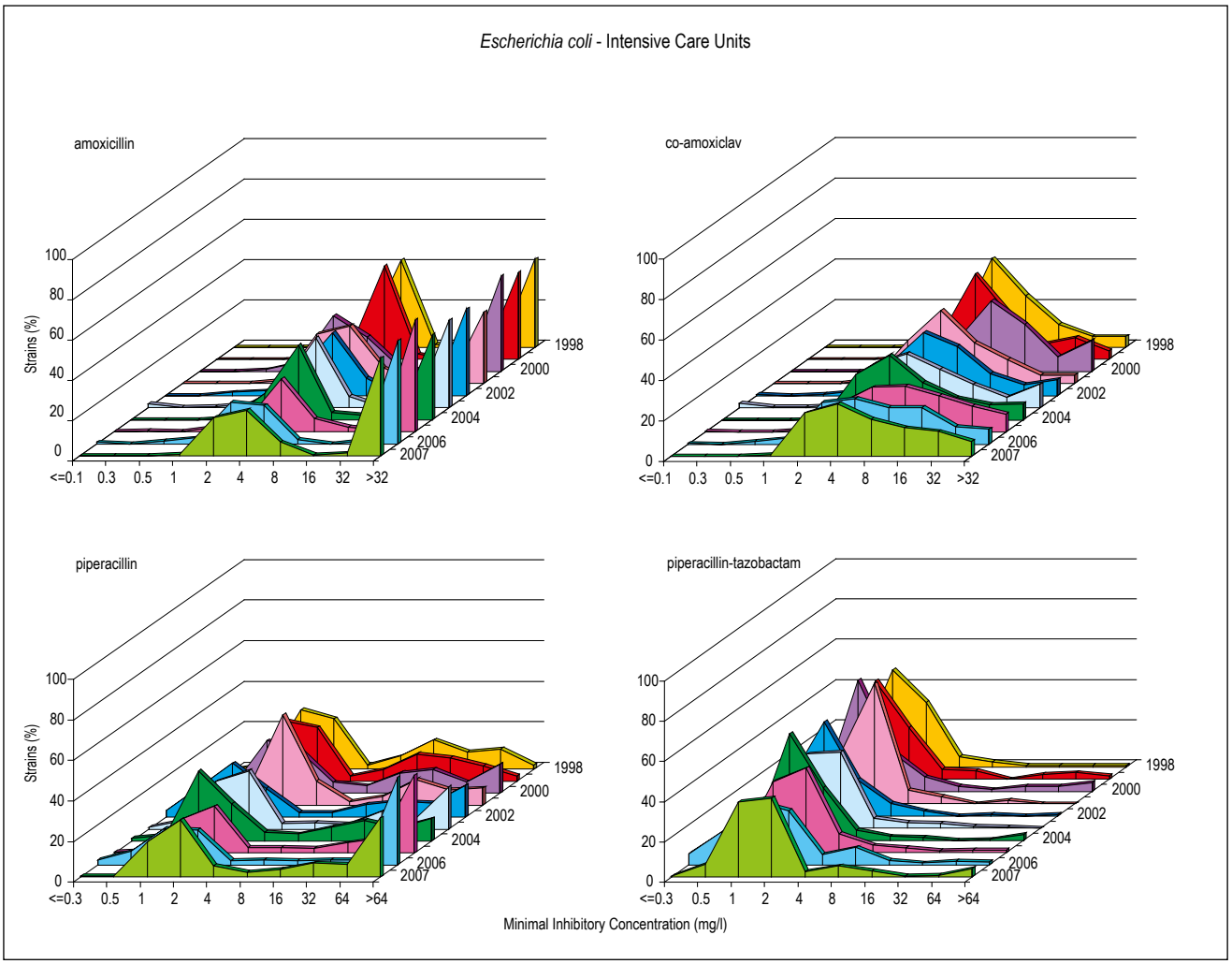


Figure 11. MIC distributions of beta-lactams for *Escherichia coli* from Intensive Care Units.

susceptible with MICs 0.5-4 mg/l and one over a broad range with MICs 8 - > 64 mg/l with a peak at MIC of 16 mg/l. This second population included susceptible (MIC < 16 mg/l) and resistant strains (MIC > 16 mg/l). From 2001 on the number of strains with MIC values close to the breakpoint became lower and an increasing number of strains with MIC > 64 mg/l could be observed. Thus the increase of resistance level calculated in 2003 could be predicted already in 2001. Piperacillin showed higher activity than amoxicillin towards the same subpopulation: the peak of MICs of piperacillin in the susceptible range was at 1-2 mg/l, that of amoxicillin at 2-4 mg/l (figure 11. Resistance to piperacillin-tazobactam was still low (5% in 2007). The MIC distribution of piperacillin-tazobactam showed an almost complete disappearance of populations resistant or intermediate to piperacillin alone, but less-susceptible strains with MICs 8-16 mg/l also emerged together with some strains with MIC > 64 mg/l, predicting a change in shape of the distribution from unimodal to bimodal.

Ceftazidime resistance in Unselected Hospital Departments was very low, but showed an increasing trend, being less than 1% until 2003 and 3% in 2007. The overall level in the Intensive Care Units and Urology Services was 1-2% and showed no significant increase. Strains from Intensive Care Units had consistently higher resistance rates for 1st and 2nd generation cephalosporins than strains from Urology Services (figure 12). Cefaclor resistance increased in both departments; resistance to cefuroxime increased in Intensive Care Units from 8% in 1998 to 15% in 2007 (figure 12). Also here the application of lower breakpoints by EUCAST for resistance (MIC > 8 mg/l) instead of the CLSI breakpoint for resistance (MIC > 16 mg/l) resulted in higher resistance rates, but the trends did not differ. The MIC distribution of cefuroxime for strains of Intensive Care Units was unimodal over a broad range (MIC 0.5 - > 16 mg/l except in 1999. Over the years the range broadened, the peak at 4 mg/l lowered (from 60% of strains in 1998 to 37% of strains in 2007) and a cluster of strains with high MICs appeared in 2007, resulting in a real bimodal distribution. The MIC distribution of cefuroxime (figure 13) for strains from Urology Services remained unimodal over a broad range. Cefotaxime and ceftazidime showed

Download from SWAB.nl | 2026-11-12 14:20

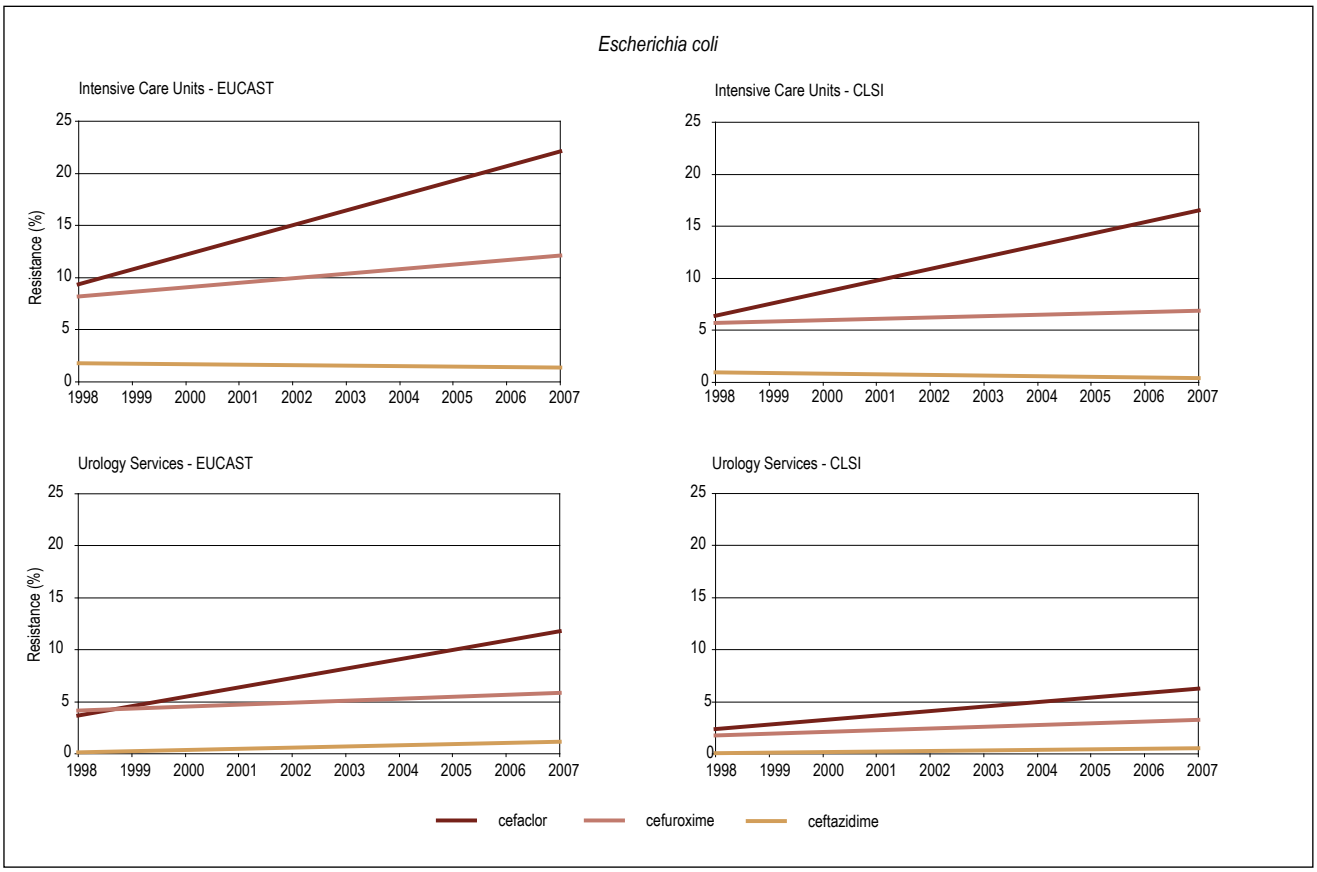


Figure 12. Trends in cephalosporin resistance of *Escherichia coli* from Intensive Care Units and Urology Services, calculated according to the breakpoints recommended by both EUCAST and CLSI.

a unimodal MIC distribution over a very small range (<= 0.12-0.5 mg/l) (figure 13).

Trimethoprim resistance increased steadily in Unselected Hospital Departments over the years from 18% to 28% (figure 10); it was 31% among urinary strains from Outpatient Clinics and from General Practice which is significantly higher. This resistance level came close to that found in Urology Services, which is quite understandable. General practitioners commonly send urine specimens for culture only in case of therapeutic failure or in chronic and complicated urinary tract infections and they refer these patients frequently to Outpatient Clinics. So, most patients have been treated with antibiotics before, often with trimethoprim or a quinolone. The level of trimethoprim resistance in Intensive Care Units increased with some fluctuations from 22% in 1998 to 33% in 2007. The level of resistance in Urology Services was always significantly higher than in Intensive Care Units, the trend increased from 31% in 1998 to 38% in 2007. The application of two different breakpoints for resistance (4mg/l versus 8 mg/l) had no effect on the outcome.

Co-trimoxazole resistance in unselected hospitals was not determined until 2007; it was 27% in 2008 and 29% in urinary strains from Outpatient Clinics and General Practice (figure 10), equal to the resistance found in Intensive Care Units (28%). The resistance in Urology Services was always higher (around 32%) with some fluctuations during the years, but without significant increase. The resistance trend in Intensive Care Units followed that of trimethoprim, being around 22% in 1998 and increasing to 28% in 2007. The MIC distributions (figure 14) for strains from Intensive Care Units showed existence of two subpopulations: one susceptible and one highly resistant, with an increasing number of resistant strains (MIC > 4 mg/l).

Nitrofurantoin resistance fluctuated around 2% in Unselected Hospital Departments, equal to the figures in the urinary strains from Outpatient Clinics and General Practice. It was higher in *E. coli* from Urology Services (3-9%). It is obvious that selection by previous use of these specific antibiotics in these patients is responsible for this higher resistance rate.

Ciprofloxacin resistance increased steadily among *E. coli* from Unselected Hospital Departments, slowly during the first four years from 1-3%, then more rapidly during the next six years: from 3% in 2001 to 10% in 2007. The resistance level in patients from Outpatient Clinics and General Practice was 11% in 2008. Increasing resistance was also observed in the Intensive Care Units from 1% in 1998 to 14% in 2007 (figure 10). The resistance level in Urology Services however increased more rapidly from

Download from SWAB.nl | 2026-11-12 14:20

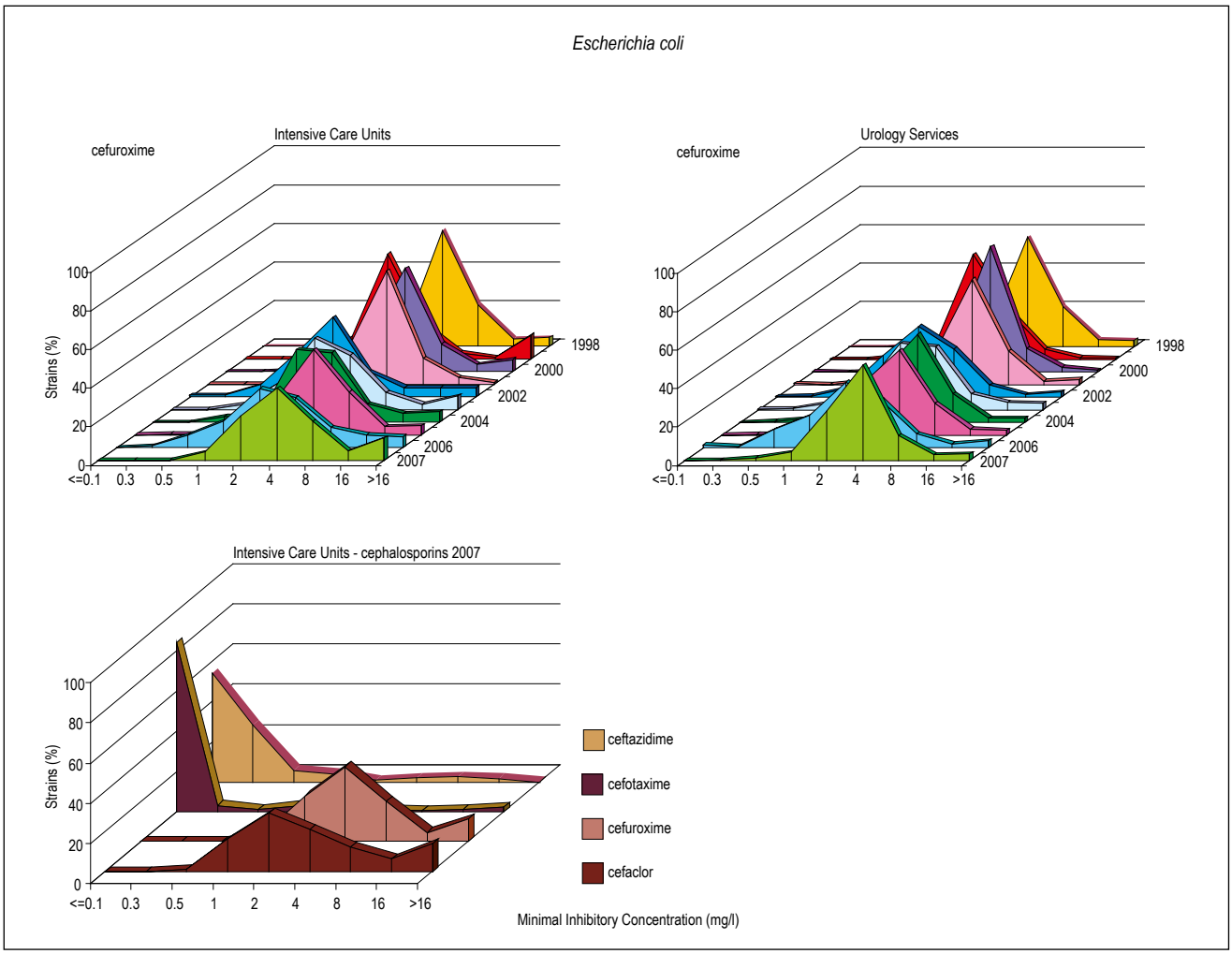
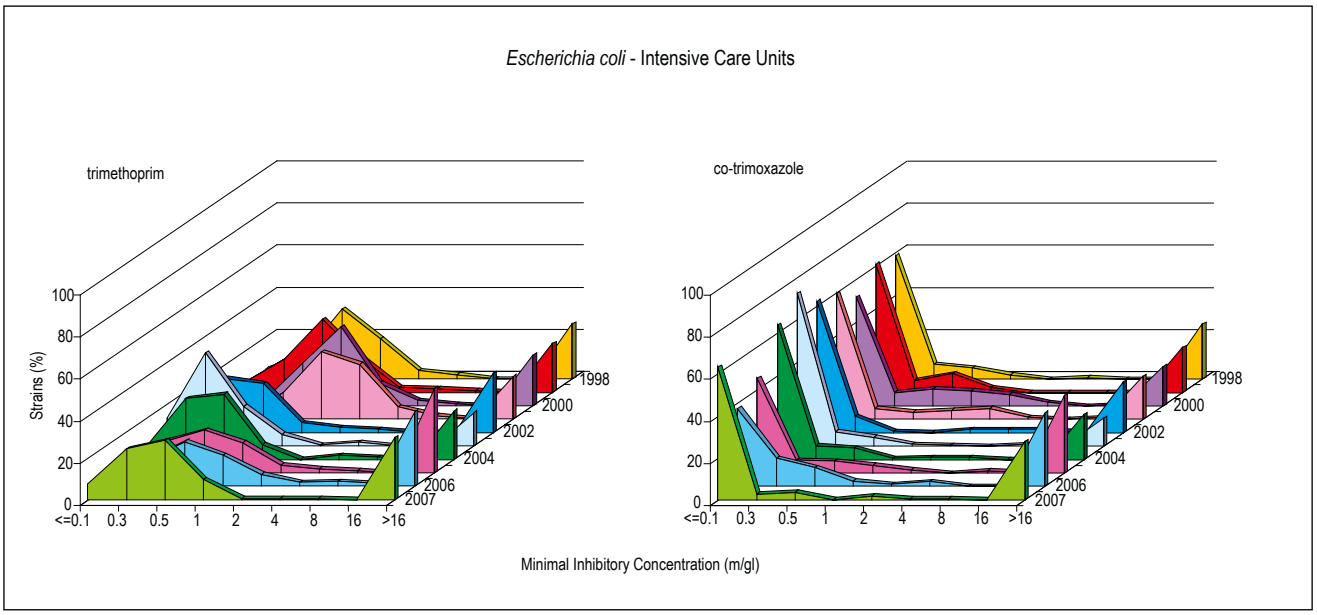


Figure 13. MIC distributions of cephalosporins for *Escherichia coli* from Intensive Care Units and Urology Services.

Figure 14. MIC distributions of trimethoprim and co-trimoxazole for *Escherichia coli* from Intensive Care Units.



Download from SWAB.nl | 2026-11-12 14:20

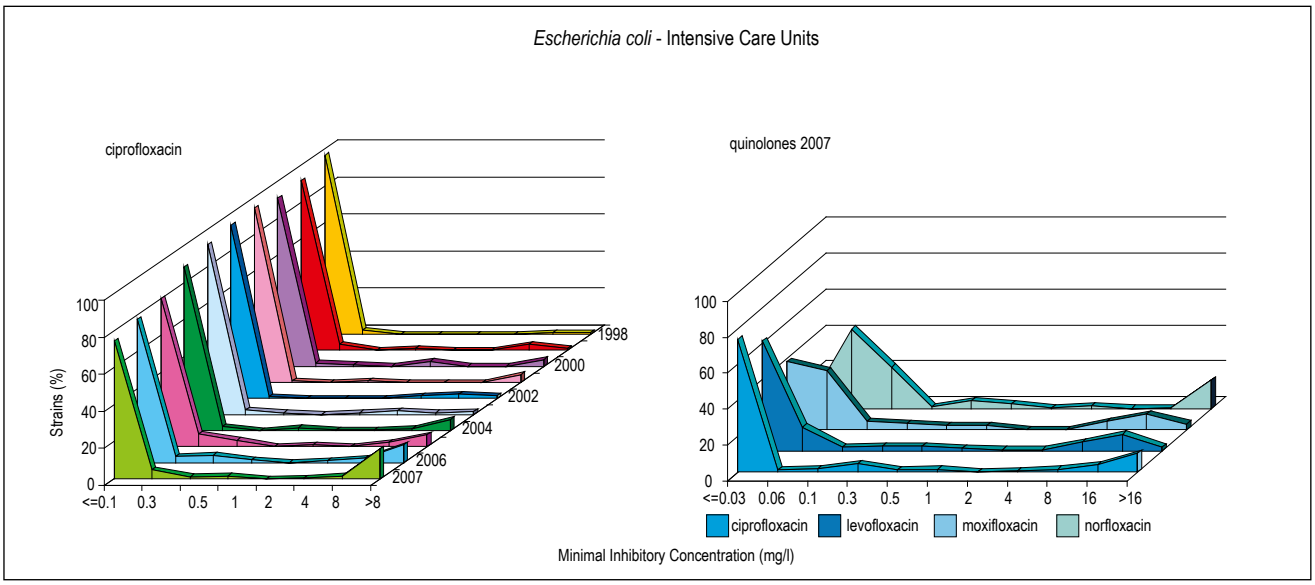
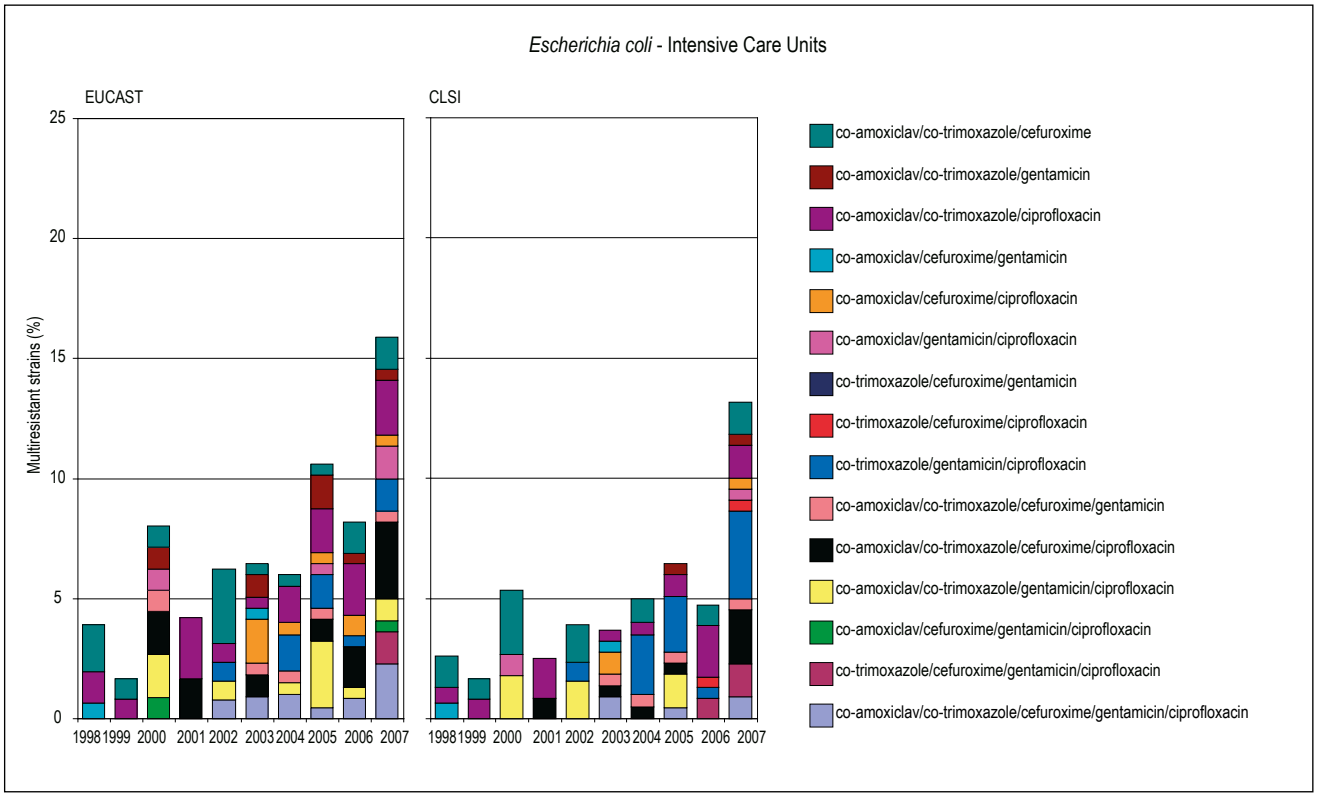


Figure 15. MIC distributions of quinolones for *Escherichia coli* from Intensive Care Units.

7% in 1998 to 19% in 2007. The resistance percentages of norfloxacin were similar, those of levofloxacin were 16% for Intensive Care isolates and 17% for Urology isolates in 2007, respectively. The application of two different breakpoints for resistance (ciprofloxacin and norfloxacin EUCAST MIC > 1 mg/l and CLSI > 2 mg/l; levofloxacin EUCAST MIC > 2 mg/l and CLSI MIC > 4 mg/l for respectively) did not influence the resistance rates. The higher resistance percentages of ciprofloxacin compared to those of levofloxacin is due to the higher breakpoint for resistance applied for levofloxacin.

The MIC distributions of the quinolones for *E. coli* from Intensive Care Units and Urology Services were bimodal with a large susceptible subpopulation over

Figure 17. Trends in multiresistance among *Escherichia coli* from Intensive Care Units, according to the breakpoints for resistance recommended by both EUCAST and CLSI.



Download from SWAB.nl | 2026-11-12 14:20

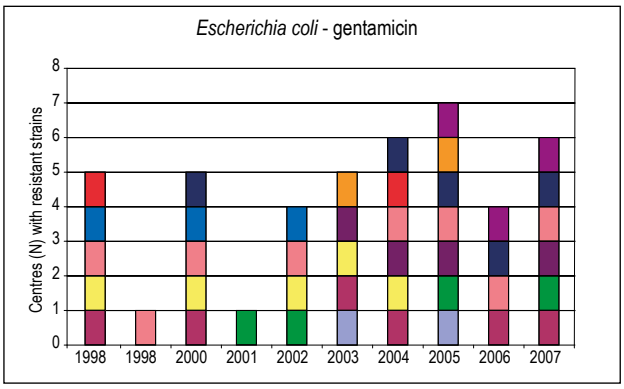


Figure 16. Number of centres with gentamicin-resistant *Escherichia coli* on Intensive Care Units. Each color represents one specific centre.

a small range (figure 15) and a small subpopulation of strains with MIC >8 mg/l. The intrinsic activity of ciprofloxacin was superior to that of the other quinolones with 74% susceptible to <0.03mg/l in 2007 compared to 61% for levofloxacin, 38% for moxifloxacin and 6% for norfloxacin. Only few strains had MICs in the intermediate area. The majority of the resistant strains had MICs > 16 mg/l. Quinolone resistance was common in all departments in 2007, but the level of quinolone-resistant *E. coli* varied between the centres from 3-25%. Gentamicin resistance in Unselected Hospital Departments was low, but increasing from 1% until 2002 to 4% in 2008; the resistance level in Intensive Care Units increased slowly from 2% in 1998 to 5% in 2007. This overall increase of gentamicin resistance was associated with an unusual high resistance level in some centres (up to 15%) (figure16). The number of centres with gentamicin-resistant strains (MIC >8 mg/l) varied considerably, only one centre in 1999 and 2001, but seven centres in 2004 en 2005, four in 2006 and six in 2007. Resistance was not associated with certain centres and it was not permanent in most centres. Therefore the increasing trend presented does not reflect a real national trend. This underlines the importance of local surveillance of resistance.

Multiresistance of *Escherichia coli* in Intensive Care Units

Resistance to three or more classes of antibiotics (multiresistance) in Intensive Care Units was recorded for various combinations at increasing levels. Before 1998 no multiresistance was observed. The annual percentages of multiresistant strains were less than 7% from 1998-2004, it increased to 11% in 2005 and it was 16% in 2007(figure 17). A total of 137 multiresistant strains were isolated between 1998 and 2007. Resistance to four and five antibiotics was recorded from 2000 on at low percentages (1-4% of the total), but it raised significantly in 2007 ($p < 0.02$), being 8% of the total amount of strains collected in that year. This increase could be only partly associated with the application of lower breakpoints for resistance according to EUCAST. A significant increase of multiresistance in 2007 (to 13.5%) was also recorded when CLSI breakpoints for resistance were applied (figure 17).

Resistance to the combination co-amoxiclav/co-trimoxazole with another drug was prevalent. These other drugs were either cefuroxime or ciprofloxacin or gentamicin (less frequent) or a combination of them. Multiresistance to the combinations co-amoxiclav/co-trimoxazole /cefuroxime and to co-amoxiclav/co-trimoxazole/ciprofloxacin was found yearly since 1998 (1–2% of the *E. coli* strains collected each year); since 2000 resistance to all four antibiotics was found and in 2002 this combination was expanded with resistance to gentamicin as well.

Similar observations were made with the co-trimoxazole combinations different from those with co-amoxiclav. Resistance to the combination co-trimoxazole / gentamicin / ciprofloxacin with or without cefuroxime emerged since 2000 in 1-1.5% of the isolates.

Summary – *Escherichia coli*

1. Using EUCAST breakpoints for resistance instead of CLSI breakpoints had impact on the resistance level of co-amoxiclav, piperacillin, cefaclor and cefuroxime.
2. Increasing resistance to amoxicillin, co-amoxiclav, piperacillin, cefaclor, cefuroxime, trimethoprim, co-trimoxazole, gentamicin and ciprofloxacin in all study populations.
3. Consistent higher resistance levels of penicillins, cephalosporins and gentamicin in Intensive Care Units compared to those in Unselected Hospital Departments and Urology Services; consistent higher resistance levels of trimethoprim and ciprofloxacin in Urology Services compared to those in Unselected Hospital Departments and Intensive Care Units. The resistance level of trimethoprim in urinary isolates of Outpatient Clinics and General Practice resembled that of Urology Services.
4. Multiresistance is increasing in Intensive Care Units.

Klebsiella pneumoniae

Co-amoxiclav resistance in *K. pneumoniae* from Unselected Hospital Departments, Outpatient Clinics and General Practice was as low as that of *E. coli* (3–6%), it fluctuated but did not increase (figure 18). Co-amoxiclav resistance in Intensive Care Units was much higher and it showed an increasing trend from18% in 1998 to 24% in 2007. Here the use of the different breakpoints had significant impact on the resistance percentages. Using CLSI breakpoints, the increase would not have

Download from SWAB.nl | 2026-11-12 14:20

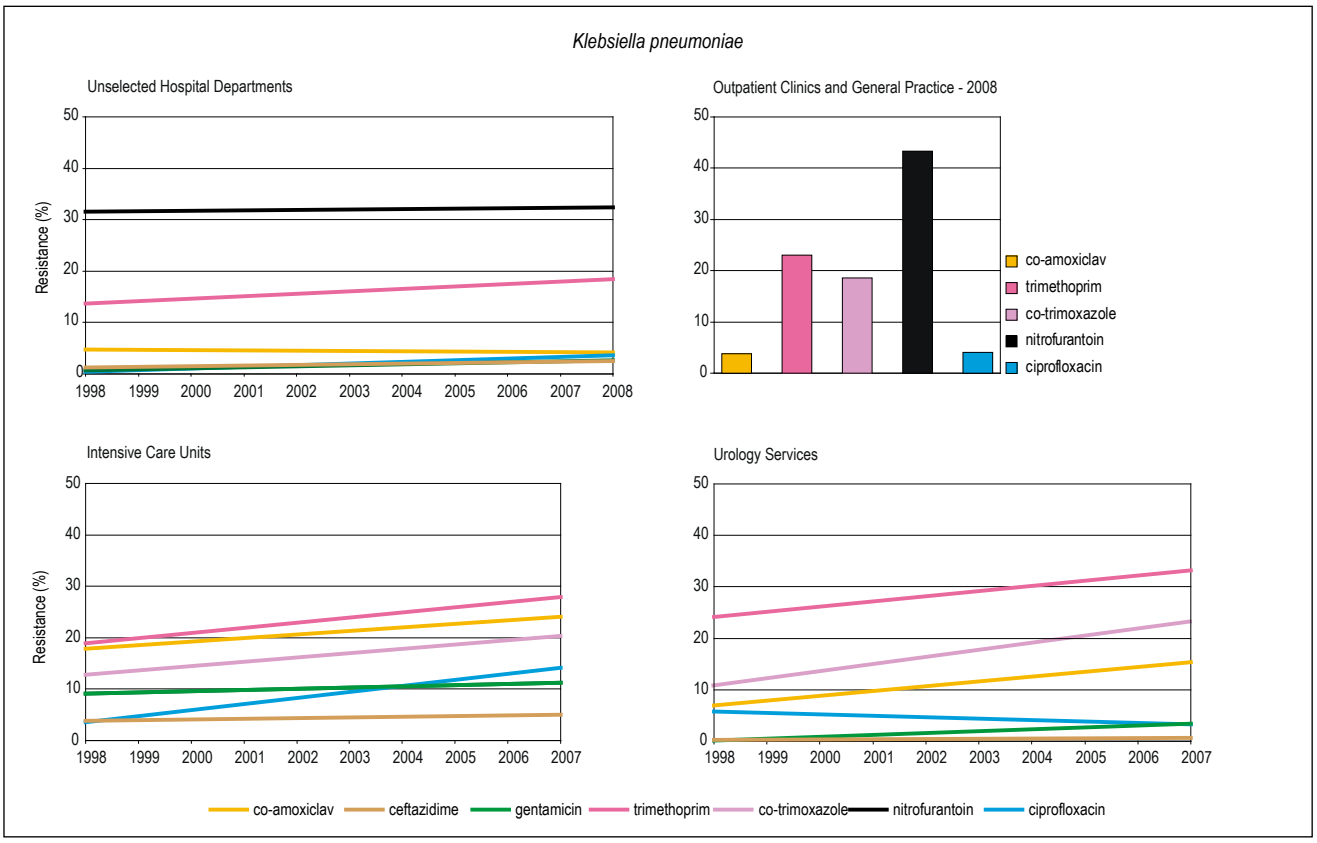
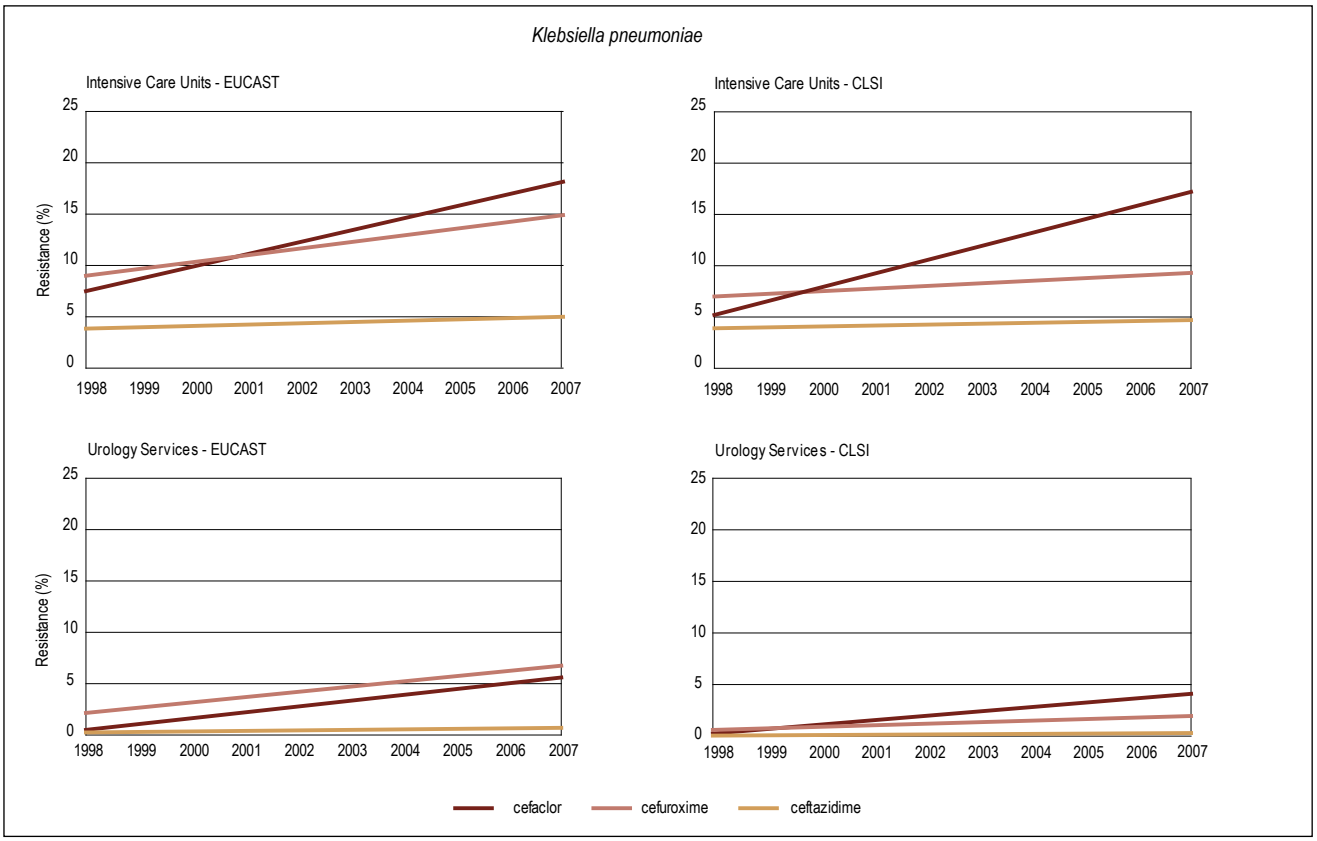


Figure 18. Trends in antibiotic resistance among clinical strains of *Klebsiella pneumoniae* from Unselected Hospital Departments, Intensive Care Units and Urology Services and among urinary strains from Outpatient Clinics and General Practice.

Figure 19. Trends in cephalosporin resistance among *Klebsiella pneumoniae* from Intensive Care Units, according to the breakpoints for resistance recommended by both EUCAST and CLSI.



Download from SWAB.nl | 2026-11-12 14:20

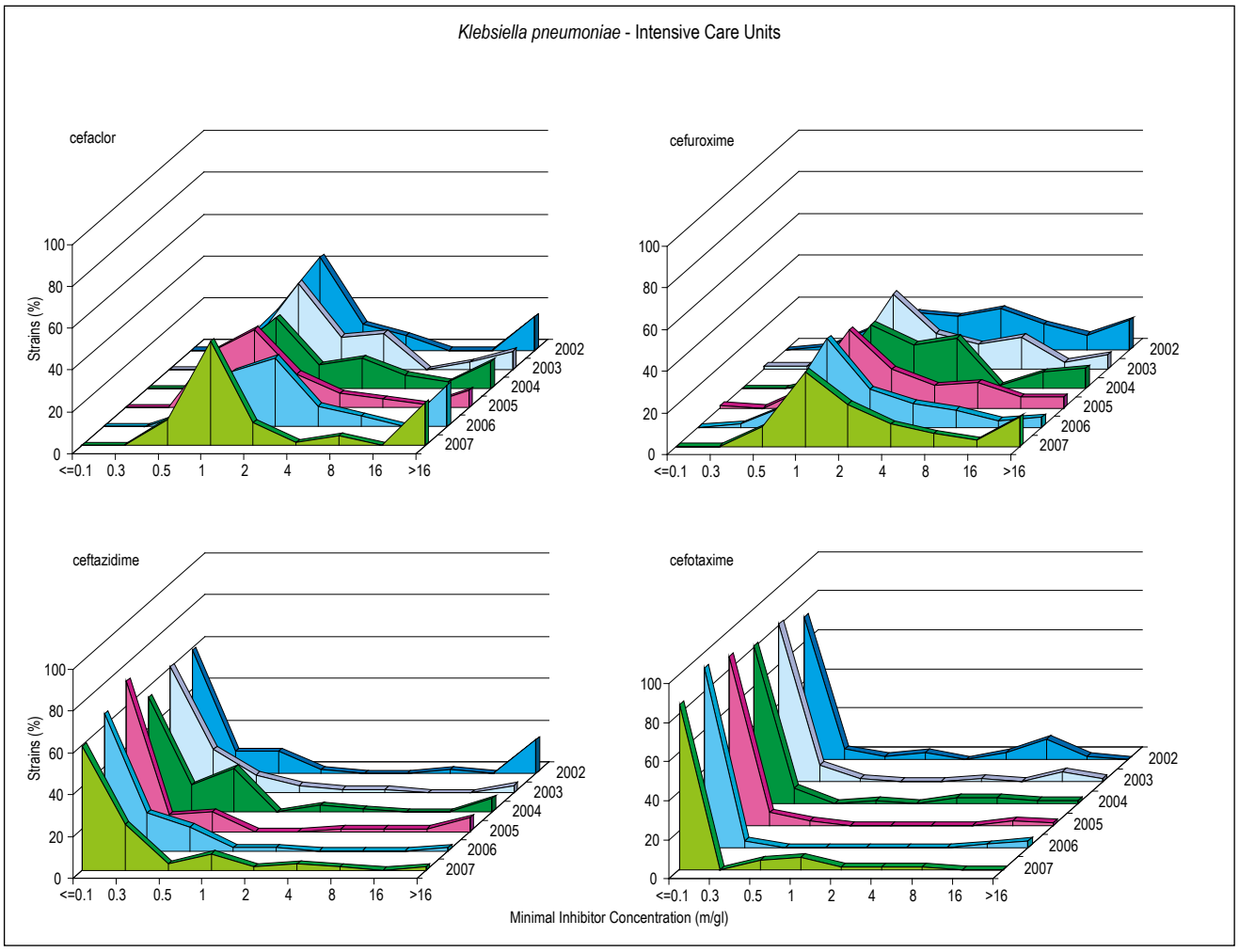


Figure 20. MIC distributions of cephalosporins for *Klebsiella pneumonia*e from Intensive Care Units.

been so large: from 15% in 1998 to 19% in 2007 (not shown). Co-amoxiclav resistance in Urology Services was lower compared to that in Intensive Care Units, but showed also an increasing trend from 7% in 1998 to 16% in 2007. Piperacillin-tazobactam resistance fluctuated between 5% and 15%, without significant increase over the years.

Resistance to cephalosporins fluctuated during the years in both Intensive Care Units and Urology Services, but the trends in Intensive Care Units (figure 19) showed an overall increase in resistance to cefaclor from 8% to 18%, to cefuroxime from 8% to 15% and to ceftazidime from 4% to 5% (figure 19). Taking CSLI breakpoints for resistance the trend of cefuroxime resistance increased less, from 7% in 1998 to 9% in 2007. The resistance trends for cefaclor and ceftazidime were hardly changed by taking CLSI breakpoints for resistance. This is easily explained by the MIC distributions of the cephalosporins (figure 20): those of cefaclor and ceftazidime were clearly bimodal with one subpopulation with MIC < 4 mg/l (susceptible according to EUCAST and CLSI criteria) and another subpopulation with MIC > 16 mg/l (resistant according to EUCAST and CLSI criteria), whereas the MIC distribution for cefuroxime showed a considerable number of strains with MIC 16 mg/l (resistant for EUCAST, but susceptible for CLSI). Ceftazidime-resistant strains were found in one Intensive Care Unit continuously since 2002 and were occasionally found in four other Intensive Care Units; resistance in Urology Services was found in four centres only once in different years. The slight increase in resistance was exclusively due to a high resistance rate in two Intensive Care Units. These strains disappeared in 2003, resulting in an overall resistance rate of around 5% or less. Resistance to ceftazidime in Unselected Hospital Departments increased from 1% in 1998 to 3% in 2008. Resistance to cefotaxime was measured since 2003 in Intensive Care Units. It decreased from 9% in 2003 to 3% in 2007, found sporadically in Urology Services. Trimethoprim resistance in Unselected Hospital Departments increased gradually from 13% in 1998 to 16% in 2008 (figure 18). This was significantly lower than that found in urinary isolates from Outpatient Clinics and General Practice (23%). The resistance level

Download from SWAB.nl | 2026-11-12 14:20

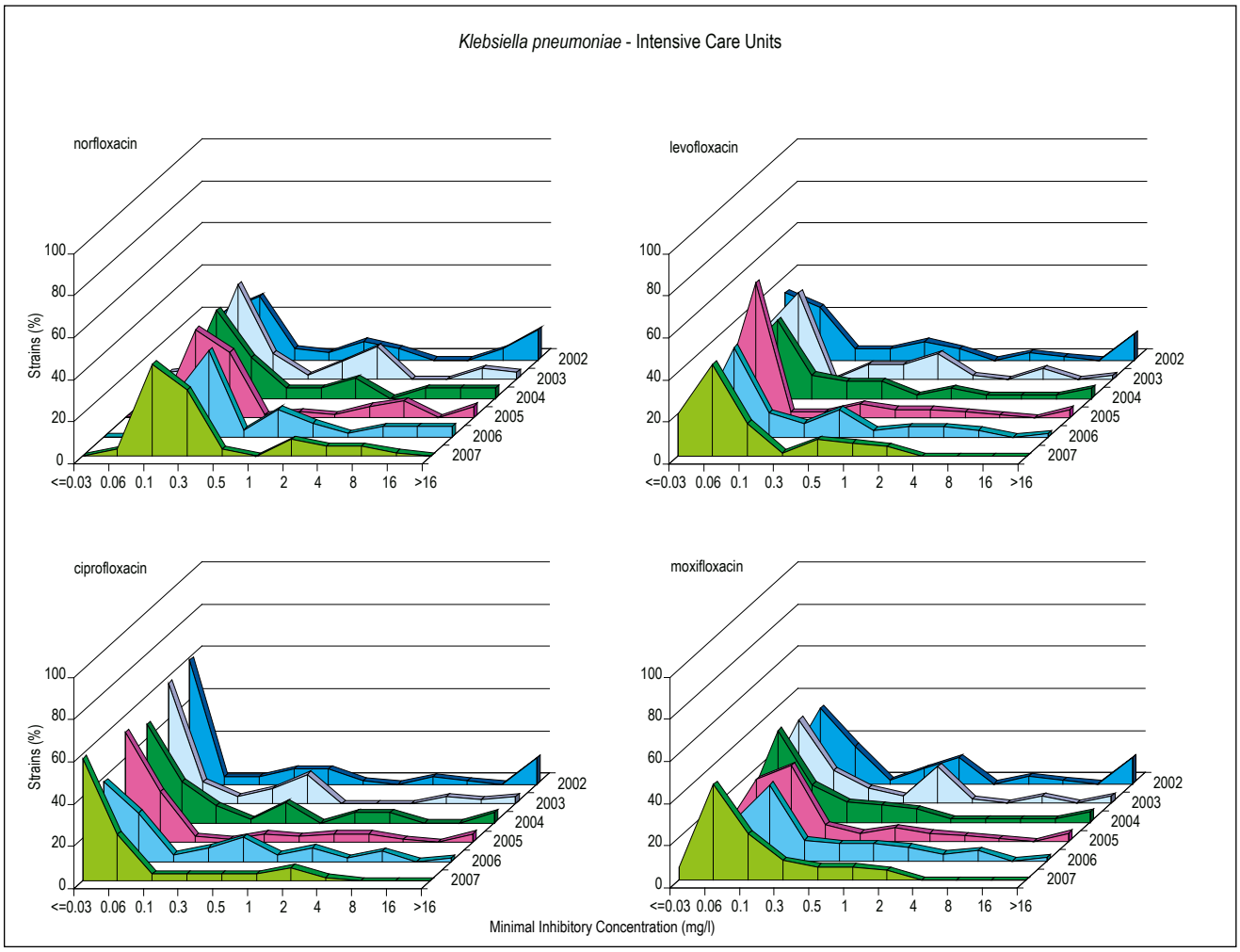


Figure 21. MIC distributions of quinolones for *Klebsiella pneumoniae* from Intensive Care Units.

in Urology Services was consistently higher and showed an increasing trend from 24% in 1998 to 33% in 2007, similar to the levels found for *E. coli*. The overall level of resistance in Intensive Care Units increased from 19% in 1998 to 28% in 2007. Trimethoprim was the drug of first choice in General Practice until 2005 and it is rarely used in Intensive Care Units. The higher resistance rates observed in urinary strains from Outpatient Clinics, General Practice and the Urology Services may reflect frequent use of this drug alone or in the combination co-trimoxazole in the previous years.

The resistance to co-trimoxazole followed the trend of trimethoprim and increased from 13% in 1998 to 20% in 2007 in Intensive Care Units and from 10% to 23% in Urology Services (figure 18). The use of EUCAST criteria influenced the resistance levels of co-trimoxazole since the breakpoint for resistance recommended by EUCAST is higher (MIC > 4 mg/l) than that recommended by CLSI (MIC > 2 mg/l). Using the CLSI breakpoint for resistance the resistance levels in Intensive Care Units and Urology Services in 2007 would be higher: 22% and 28% respectively. Co-trimoxazole is an alternative drug combination for Klebsiella infections in Intensive Care Units and it is often used for complicated urinary tract infections in Urology Services and Paediatric departments. Use of co-trimoxazole in these settings should be reconsidered in view of the high resistance levels found.

Nitrofurantoin resistance fluctuated in Unselected Hospital Departments around 32% without a visible trend. However, that in urinary strains of Outpatient Clinics and General Practice was 43% in 2008 (figure 18). The resistance level in Urology Services was higher than 50% (not shown).

Gentamicin resistance in Unselected Hospital Departments was low, but increased slowly from 1% in 1998 to 3% in 2008 (figure 18). Gentamicin-resistant strains were observed continuously in two Intensive Care Units from 1999 onwards and sporadically in four others, resulting in large overall fluctuations in gentamicin resistance rates over the years of surveillance with an overall increasing trend from 9% in 1998 to 11% in 2007. These figures are therefore not representative for all Intensive Care Units. This underlines the need for local

Download from SWAB.nl | 2026-11-12 14:20

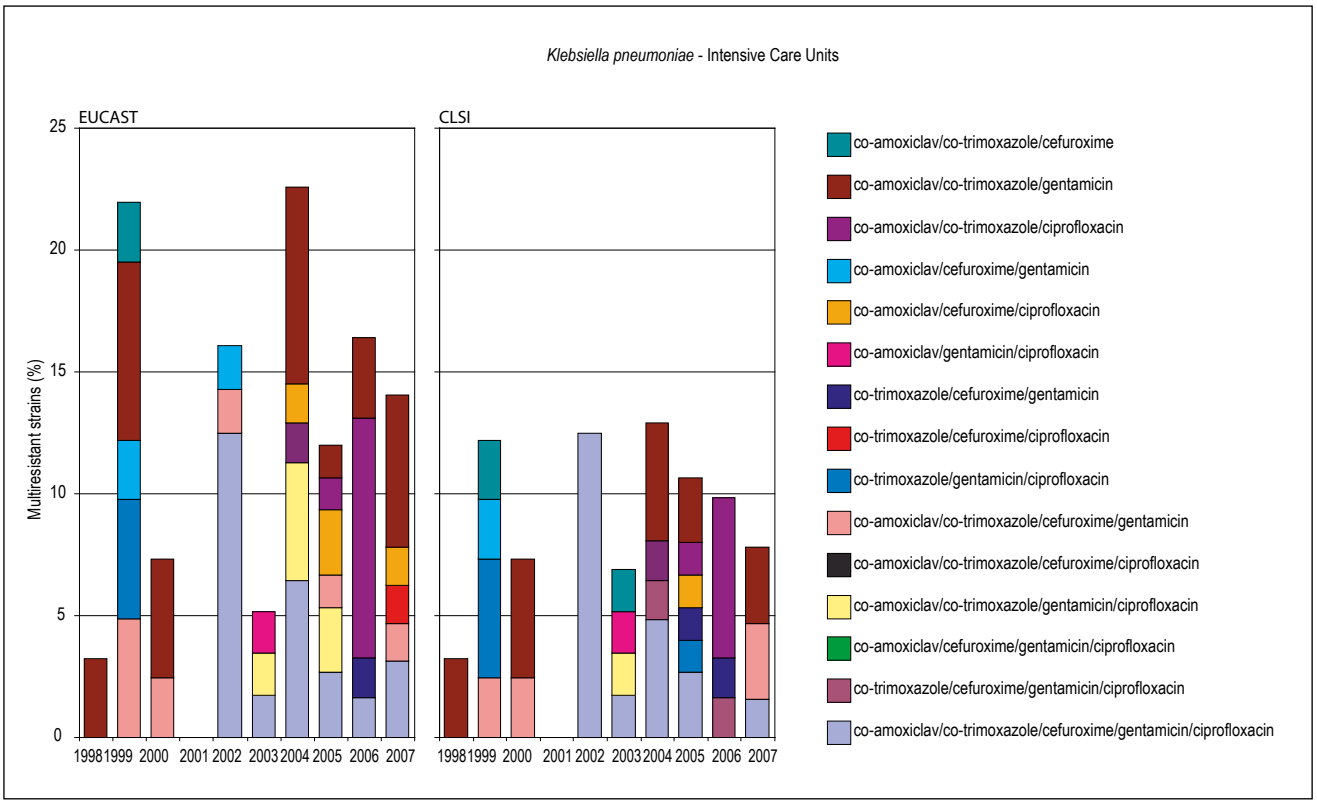


Figure 22. Trends in multiresistance among *Klebsiella pneumonia*e from Intensive Care Units, according to the breakpoints for resistance recommended by both EUCAST and CLSI.

surveillance. Gentamicin resistance in Urology Services was rare.

Ciprofloxacin resistance among *K. pneumoniae* in Unselected Hospital Departments increased slowly, being lower than 1% until 2001 to 4% in 2008 (figure 18). Ciprofloxacin resistance in Intensive Care Units showed an increasing trend from 4% in 1998 to 14% in 2007. Resistant strains were found in five to eight centres from the beginning; from 2003 onwards ciprofloxacin-resistant strains were isolated in all centres. In contrast, ciprofloxacin resistance in Urology Services decreased from 7% in 1998 to 3% in 2007, a level comparable with that in Unselected Hospital Departments and Outpatient Clinics and General Practice in 2008. The use of EUCAST criteria affected the resistance level for ciprofloxacin. Using the CLSI criteria, the resistance level in 2007 would be 8% instead of 14% by applying EUCAST criteria. The MIC distribution for ciprofloxacin showed a number of strains with MICs = 2 mg/l which is considered intermediate using CLSI criteria and resistant when using EUCAST criteria (figure 20). The MIC distributions of all quinolones tested showed a susceptible subpopulation over a broad range (MIC ≤ 0.03 – 0.5 mg/l) and another subpopulation with MIC 1-8 mg/l, whereas only few strains had MICs ≥16 mg/l (figure 21). This differed from the MIC distributions of quinolones for *Escherichia coli* where a real bimodal distribution was observed. The intrinsic activity of ciprofloxacin to *Klebsiella pneumoniae* was superior to that of the other quinolones with 58% susceptible to ≤0.03mg/l in 2007 compared to 20% for levofloxacin, 6% for moxifloxacin and 0% for norfloxacin (figure 21).

Multiresistance of *Klebsiella pneumoniae* in Intensive Care units

Multiresistance (resistance to three or more classes of antibiotics) in Intensive Care Units was recorded yearly except in 2001 at varying percentages (3–23% of all *K. pneumoniae* strains) (figure 22). A real trend was not visible, although the proportion (% multiresistant of the total number) seems to become more consistent (approx. 15%) from 2004 onwards. The highly fluctuating numbers of multiresistant strains may be associated with high resistance levels for e.g. ciprofloxacin and gentamicin in some Intensive Care Units as described earlier. The antibiotic combinations for which resistance was recorded differed in some way from those found in *E. coli* strains. For *E. coli* the combinations co-amoxiclav/co-trimoxazole with either cefuroxime or ciprofloxacin were observed frequently, whereas the combination co-amoxiclav/co-trimoxazole/gentamicin for *K. pneumoniae* predominated. Unlike in *E. coli* the proportion of strains resistant to four or five classes of antibiotics was higher (3-14% of all *K. pneumoniae* isolates).

The high multiresistance levels are only partly due

Download from SWAB.nl | 2026-11-12 14:20

to application of EUCAST criteria instead of CLSI criteria. Application of CLSI breakpoints recorded multiresistance percentages from 3-13% during the study period.

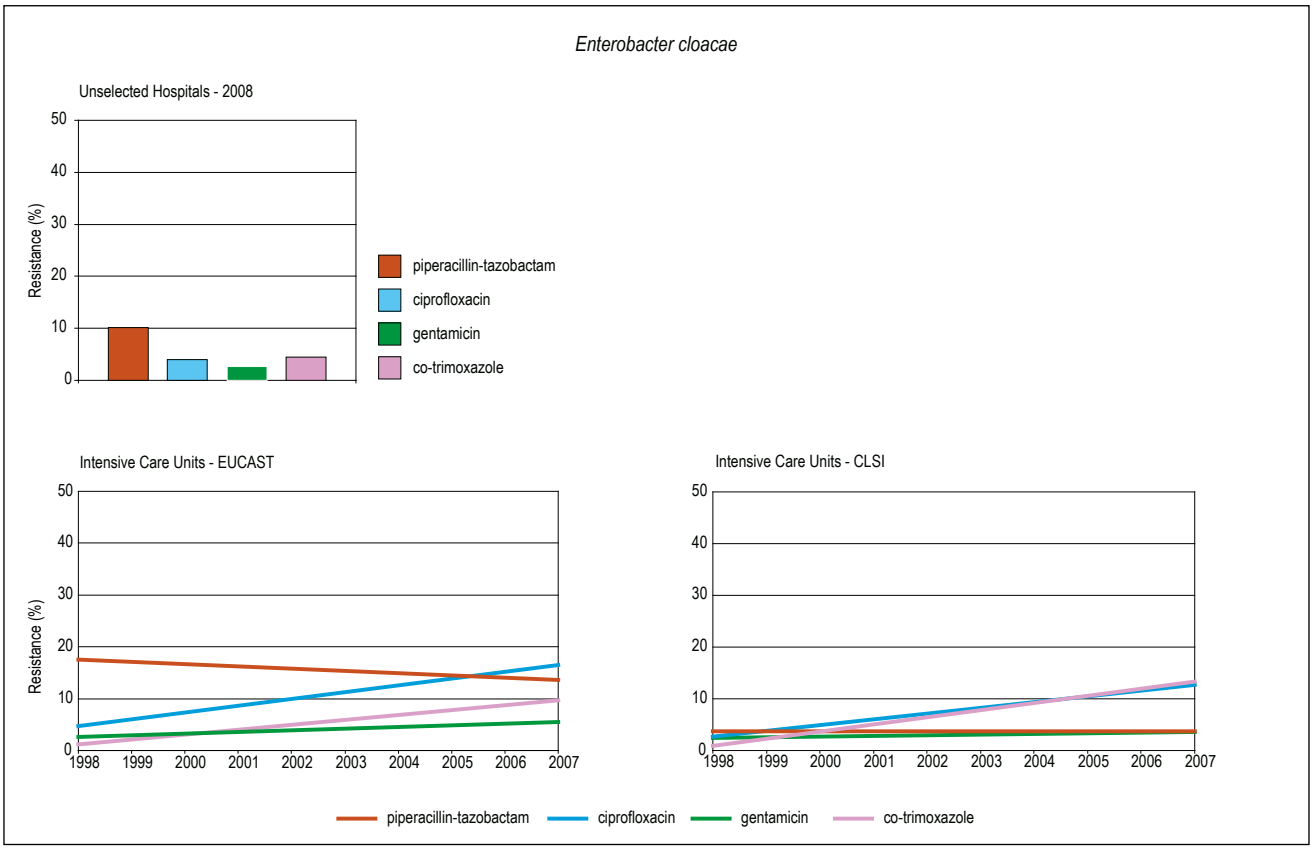
Summary – *Klebsiella pneumoniae*

1. Using EUCAST breakpoints for resistance instead of CLSI breakpoints had impact on the resistance level of co-amoxiclav, cefaclor, cefuroxime, co-trimoxazole and ciprofloxacin.
2. Increasing resistance to co-amoxiclav, cefaclor, cefuroxime, trimethoprim and co-trimoxazole in Intensive Care Units.
3. Consistent higher resistance level of co-amoxiclav, cephalosporins, gentamicin and ciprofloxacin in Intensive Care Units compared to Unselected Hospital Departments and Urology Services; consistent higher resistance level to nitrofurantoin in Urology Services and urinary isolates of Outpatient Clinics and of General Practice compared to Unselected Hospital Departments.
4. Multiresistance of 14% in Intensive Care Units.

Enterobacter cloacae

The number of strains isolated from patients in Urology Services was less than 20 yearly and therefore they were excluded for comparison with the results from Intensive Care Units and Unselected Hospital Departments. Between 1998 and 2007, 90% or more of *E. cloacae* strains from Intensive Care Units were resistant to co-amoxiclav. Piperacillin resistance in Intensive Care Units fluctuated around 28% (not shown); resistance to the piperacillin/tazobactam combination varied considerably , ranging from 6-23%, but the overall trend was decreasing from 18% in 1998 to 14% in 2007 (figure 23).The fluctuation was clearly related to the emergence of resistant strains in some Intensive Care Units. These strains were recorded occasionally in all centres, often only for a short period and not every year. Therefore, the overall resistance percentage does not reflect the general situation in Intensive Care Units and does not indicate a trend. If CLSI breakpoints had been used, the resistance percentages would have been 4% over the whole study period. The resistance level in Unselected Hospital Departments was 10% in 2008, which is lower than that in Intensive Care Units (figure 23). Meropenem resistance was exceptional in Unselected Hospital Departments (0.1% in 2008) and only once found in 2003 (3%) in Intensive Care Units.

Figure 23. Trends in antibiotic resistance among urinary strains of *Enterobacter cloacae* from Unselected Hospitals and among clinical strains from Intensive Care Units. The latter were calculated according to the breakpoints recommended by both EUCAST and CLSI.



Download from SWAB.nl | 2026-11-12 14:20

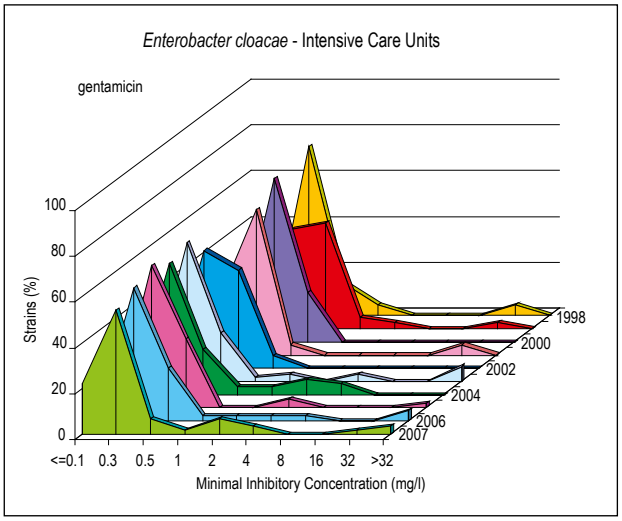
Cephalosporin (2nd, 3rd and 4th generation) resistance among *E. cloacae* strains from Intensive Care Units was approx 30% or more, except for cefepime (less than 5%) during the whole study period (not shown). Application of the EUCAST breakpoint for resistance (MIC > 8 mg/l) instead of the CLSI breakpoint (MIC > 16 mg/l) did influence the resistance levels of all cephalosporins, but they would have been then approx. 20%, which is still high. Any cephalosporin is therefore not recommended as empiric therapy in Intensive Cares with circulating *E. cloacae* strains.

Co-trimoxazole resistance in Unselected Hospital Departments was 4.5% in 2008. The resistance level in Intensive Care Units increased with annual fluctuations from 1% in 1998 to 10% in 2007 (figure 23). Application of the EUCAST breakpoint for resistance did influence the resistance percentages, because the CLSI breakpoint for resistance to co-trimoxazole is lower (MIC > 2 mg/l) than that recommended by EUCAST (MIC > 4 mg/l). Then the resistance trend should have increased from 1% in 1998 to 13% in 2007 (figure 23). Such differences can show up when the MIC values of the strains are close to the breakpoints.

Gentamicin resistance was 3% in Unselected Hospital Departments, that in Intensive Care increased from 3% in 1998 to 6% in 2007. When the CLSI breakpoint for resistance (MIC > 8 mg/l) had been applied, the resistance level of gentamicin would have been 4% during the whole study period and the slight increase in gentamicin resistance observed with application of the EUCAST breakpoint for resistance (MIC > 4 mg/l) should not have been noticed. Until 2002 the MIC distribution for gentamicin was bimodal with a susceptible subpopulation with MIC < 2 mg/l) and a resistant one with MIC > 16mg/l (figure 24). From 2003 onwards, small subpopulations with MIC = 8 mg/l appeared; these strains were recorded resistant by EUCAST, and still susceptible according to CLSI criteria (figure 24). Tobramycin resistance in Unselected Hospital Departments was 4% in 2008, the trend in Intensive Care Units was increasing from 1% in 1999 to 10% in 2007 (figure 23). There was no complete cross resistance between the two aminoglycosides. Amikacin resistance was exceptional in both Unselected Hospital Departments (0.1% in 2008) and in Intensive Care Units (3% in 2000 and 2003).

Ciprofloxacin resistance in Unselected Hospital Departments was 4% in 2008, the trend in Intensive Care Units showed an increase from 5% in 1998 to 16% in 2007. Use of the breakpoint for resistance recommended by CLSI (MIC > 2 mg/l) instead of EUCAST (MIC > 1 mg/l) should have recorded lower resistance levels (3-13%) during the study period.

Figure 24. MIC distributions of gentamicin for *Enterobacter cloacae* from Intensive Care Units.t



Summary – *Enterobacter cloacae*

1. Using EUCAST breakpoints for resistance instead of CLSI breakpoints had impact on the resistance percentages to piperacillin/tazobactam, cephalosporins, co-trimoxazole, gentamicin and ciprofloxacin.
2. Higher resistance rates of piperacillin-tazobactam, co-trimoxazole, gentamicin and ciprofloxacin in Intensive Care Units compared with Outpatients Clinics and General Practice.
3. Increasing resistance to co-trimoxazole, gentamicin and ciprofloxacin in Intensive Care Units.
4. Decreasing resistance to piperacillin-tazobactam in Intensive Care Units.
5. Slight increase of gentamicin resistance in Intensive Care Units.
6. No resistance to imipenem and meropenem.

Proteus mirabilis

Amoxicillin resistance in Unselected Hospital Departments showed a continuous increase, from 13% in 1998 to 24% in 2008. Amoxicillin resistance in Intensive Care Units fluctuated, but the trend indicated an increase from 19% in 1998 to 37% in 2007 (figure 25). Amoxicillin resistance in Urology Services increased from 18% in 1998 to 35% in 2007. The distribution of MICs of the strains from the Urology Services was bimodal and showed two subpopulations: a susceptible one over a small range in most years (MIC 0.5-1.0 mg/l) and a resistant one with MICs >8 mg/l (figure 26). In some years (2002, 2004, 2005) the range for the susceptible population broadened (0.2-4 mg/l) and resistant strains with MIC 16-32 mg/l emerged with a clear shift to high resistance in the next year.

Co-amoxiclav resistance in Unselected Hospital

Download from SWAB.nl | 2026-11-12 14:20

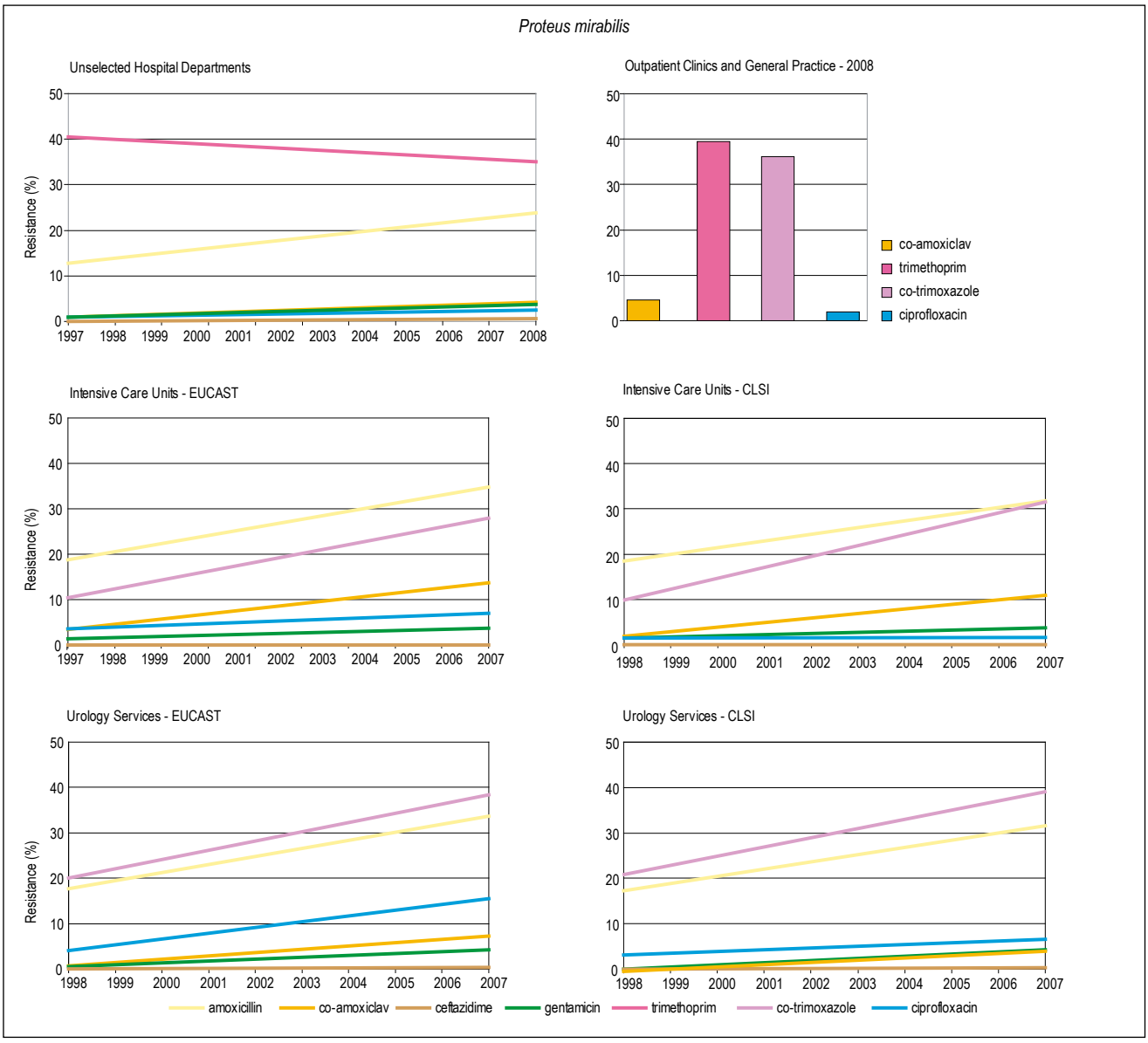


Figure 25. Trends in antibiotic resistance among clinical strains of *Proteus mirabilis* from Unselected Hospital Departments, Intensive Care Units and Urology Services and among urinary strains from Outpatient Clinics and General Practice. Trends in Intensive Care Units and Urology Services were calculated according to the breakpoints for resistance recommended by both EUCAST and CLSI.

Departments was similar to that in Urology Services until 2002 (1-2%). Thereafter the resistance level in Unselected Hospitals increased to 4% in 2008 and that in Urology Services to 7%. The resistance level among strains from Outpatient Clinics and General Practice was 5% in 2008. Co-amoxiclav resistance in Intensive Care Units was only occasionally observed from 1998-2000. From 2001 onwards co-amoxiclav-resistant strains emerged with the highest level of 14% in 2007. The MIC distribution of co-amoxiclav showed a change in 2000 and 2001 compared with the years before, including a shift to the right and flattening of the peak at 1 mg/l with appearance of small subpopulations with MIC 4-16 mg/. This continued in the following years resulting in a 6% resistance in 2003 and further. So, the increase of resistance observed in 2003 could already be predicted three years earlier by analyzing the MIC distributions. This underlines the importance of quantitative susceptibility testing. The resistance percentages of both amoxicillin and co-amoxiclav should have been 3-4% lower when the CLSI breakpoint for resistance had been applied (figure 25).

Cefuroxime resistance in Intensive Care Units fluctuated between 3% and 8%, and in Urology Services between 1% and 4%. Ceftazidime resistance in *P. mirabilis* was less than 1% in all hospital departments. Cefotaxime resistance was sporadically found in Intensive Care Units.

Trimethoprim resistance in *P. mirabilis* in Unselected Hospital Departments showed a decreasing trend from

Download from SWAB.nl | 2026-11-12 14:20

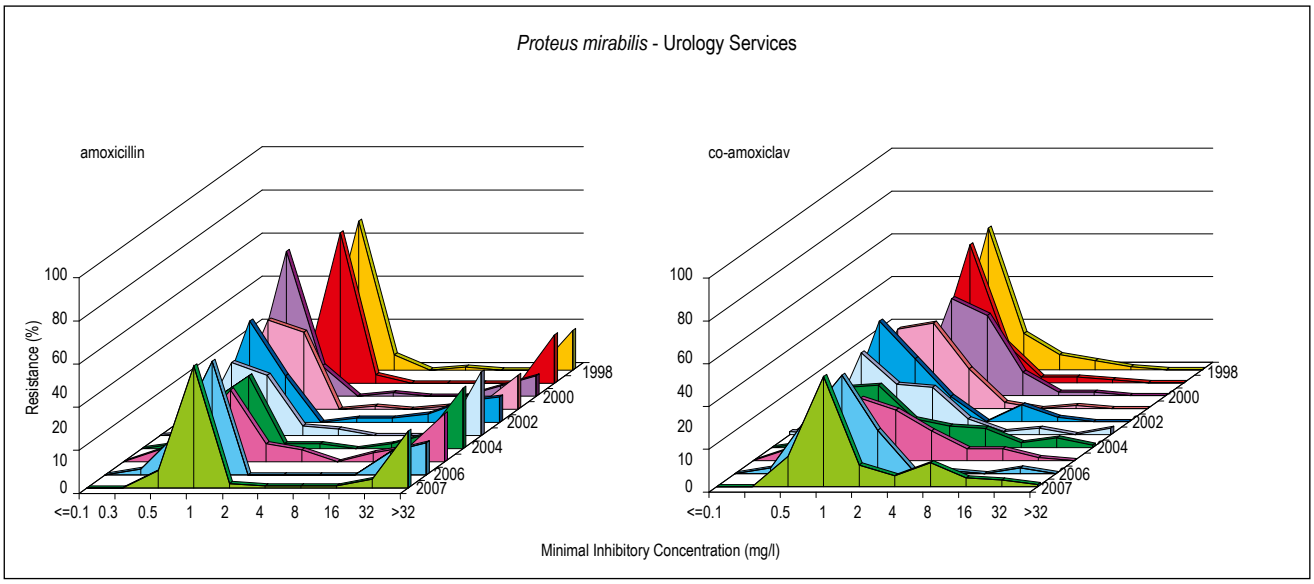


Figure 26. MIC distributions of amoxicillin and co-amoxiclav for *Proteus mirabilis* from Urology Services.

40% in 1998 to 35% in 2008, although with some fluctuations. The resistance level among urinary strains from Outpatient Clinics and General Practice was 39% in 2008, equaling the levels found in Urology Services in 2003, 2004 and 2006, but the resistance level in the latter rose to 54% in 2007 (not shown). This level should have been 47% when the CLSI breakpoint for resistance (MIC > 8 mg/l) instead of that of EUCAST (MIC > 4 mg/l) had been applied.

Co-trimoxazole resistance in Outpatient Clinics and General Practice was 36% in 2008 (figure 25), which is as high as the levels found in Urology Services two years earlier (increasing trend from 21% in 1998 to 41% in 2007). The resistance levels in Intensive Care Units were consistently lower, but the trend was also increasing from 20% in 1998 to 26% in 2007. The resistance percentages to co-trimoxazole turned out to be approx 2% lower when using the EUCAST breakpoint for resistance (MIC > 4 mg/l) compared to that of CLSI (MIC > 2 mg/l) (figure 25).

Gentamicin resistance increased slowly in all departments from 1% in 1998 to 4% in 2007 and 2008.

Ciprofloxacin resistance among *P. mirabilis* in Unselected Hospital Departments increased from 1% to 2% during the study period and was equal to that found in urinary isolates from Outpatient Clinics and General Practice. The overall resistance level in Intensive Care Units rose from 4% in 1998 to 7% in 2007, but it was not found every year and not in all centres, so a significant trend was not observed. The resistance level in Urology Services increased significantly with a trend from 4% in 1998 to 16% in 2007. These resistance percentages should be 3% and 7% respectively when the CLSI breakpoint for resistance (MIC > 2 mg/l) had been used instead of that of EUCAST (MIC > 1 mg/l).

Summary – *Proteus mirabilis*

1. Using EUCAST breakpoints for resistance instead of CLSI breakpoints had impact on the resistance percentages to co-amoxiclav, trimethoprim, co-trimoxazole and ciprofloxacin.
2. Increasing resistance to amoxicillin co-amoxiclav and gentamicin in all study populations.
3. Decreasing resistance to trimethoprim in Unselected Hospital Departments
4. Increasing resistance to co-trimoxazole in Intensive Care Units
5. Increasing resistance to ciprofloxacin in Urology Services.

Pseudomonas aeruginosa

Piperacillin resistance among *P. aeruginosa* isolated in Unselected Hospitals was not routinely recorded until 2007. The resistance level in 2008 was 3% (not shown). Resistance in Intensive Care Units was not found until 2000; then an increasing number of Intensive Care Units delivered resistant strains, resulting in an overall increasing trend to 17% in 2007. This was also found when applying the CLSI criteria with higher breakpoint of resistance (MIC > 64 mg/l instead of MIC > 16 mg/l indicated by EUCAST), although the percentage should be somewhat lower (11% resistance). Piperacillin resistance in Urology Services was accidental, fluctuating between 2% and 7%, affecting 2-3 centres in 2002-2004. The resistance to piperacillin-tazobactam followed that of piperacillin (not shown). The MIC distributions of piperacillin are given in figure 28. They were unimodal in from 1998 to 2000. In 2001, a shoulder in the area MIC 8-16 mg/l and a small subpopulation of strains

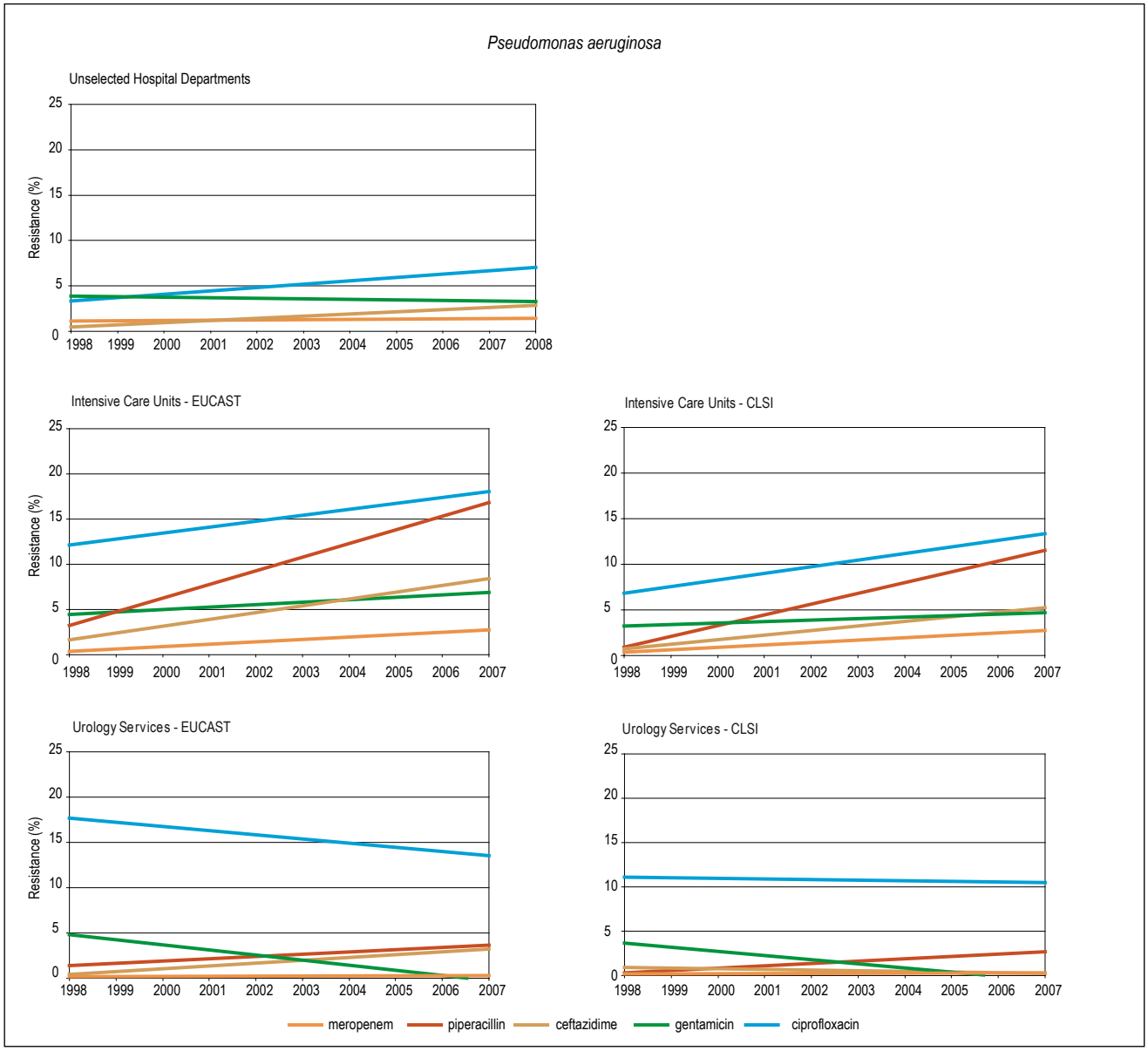
Download from SWAB.nl | 2026-11-12 14:20

with MIC > 64 mg/l emerged. The following year the resistant subpopulation had increased and the distribution became bimodal. In 2005, the distribution broadened over the area 0.25-8 mg/l with a shift of the median to higher MICs and in 2007 a shoulder appeared again in the range 8-32 mg/l, suggesting the next shift to the right. The same phenomenon was observed for piperacillin-tazobactam.

Meropenem resistance among *P. aeruginosa* remained less than 2% in Unselected Hospital Departments during the years. It was less than 2% in Intensive Care Units until 2006, but 4.5% resistance was recorded in 2007. It appeared that resistant strains were found in five of 14 centres only, so this resistance figure reflected a local problem in some Intensive Care Units and was therefore not representative for The Netherlands as a whole. Meropenem resistance was found only once in Urology Services in 2003.

Ceftazidime resistance among *P. aeruginosa* isolated in Unselected Hospital Departments and in Urology Services was consistently low (0-5%) without a trend. Ceftazidime resistance in Intensive Care Units fluctuated, but the trend was increasing from 2% in 1998 to 9% in 2007. An incidental 12% resistance was recorded in 2002 because of an unusual high resistance rate in five centres. This resistance level was not representative for Intensive Care Units in general, but reflected a local problem with a highly resistant population.

Figure 27. Trends in antibiotic resistance among clinical strains of *Pseudomonas aeruginosa* from Unselected Hospital Departments, Intensive Care Units and Urology Services. Trends in Intensive Care Units and Urology Services were calculated according to the breakpoints for resistance recommended by both EUCAST and CLSI.



Download from SWAB.nl | 2026-11-12 14:20

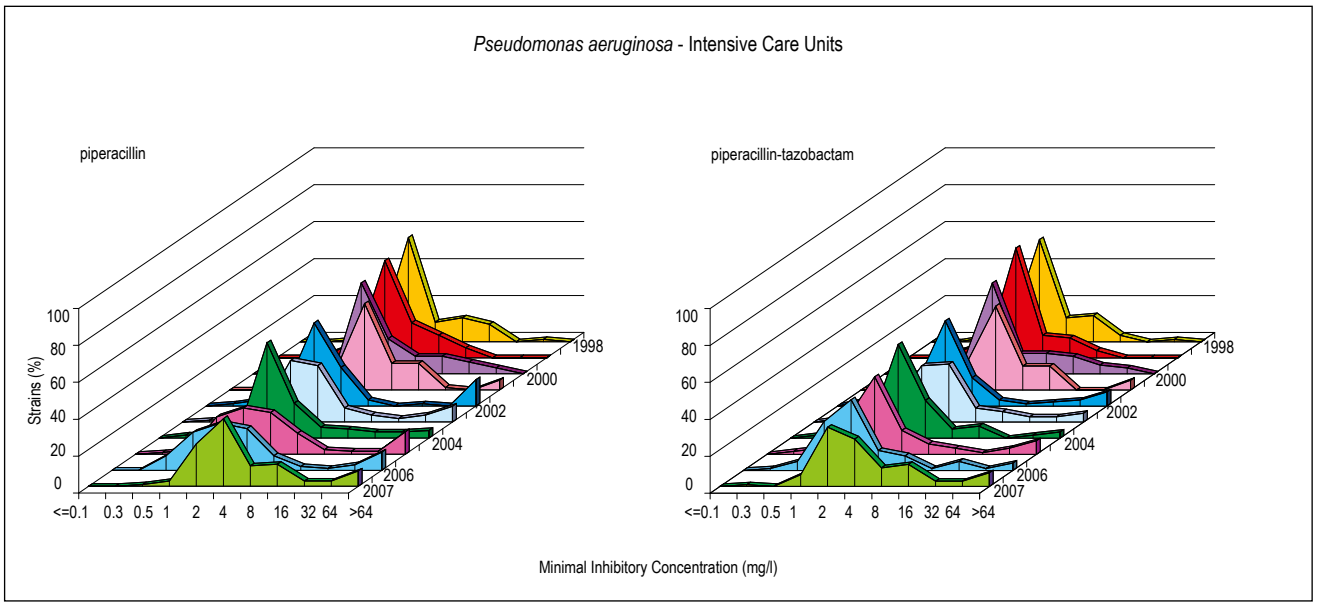
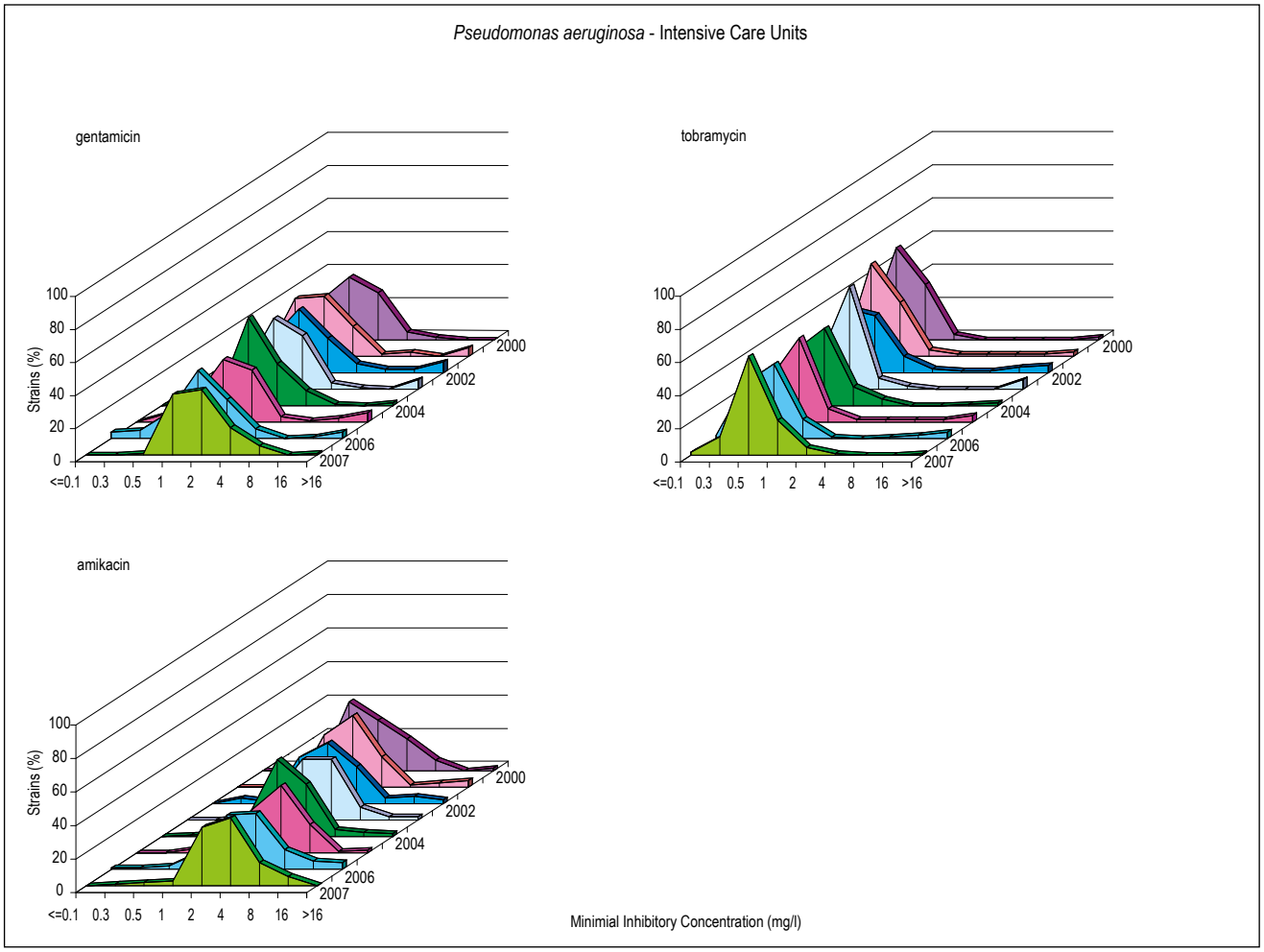


Figure 28. MIC distributions of piperacillin and piperacillin-tazobactam for *Pseudomonas aeruginosa* from Intensive Care Units.

Figure 29. MIC distributions of aminoglycosides for *Pseudomonas aeruginosa* from Intensive Care Units.



Download from SWAB.nl | 2026-11-12 14:20

Gentamicin resistance fluctuated in Unselected Hospital Departments between 2-4% during the years without a trend. Gentamicin resistance was found sporadically in some Urology Services. Resistance was found yearly in one to six Intensive Care Units, responsible for the fluctuations in the overall resistance rate from 2-8%. Amikacin- and tobramycin resistance in Unselected Hospital Departments was 1% in 2008; amikacin resistance in Intensive Care was less than 4% during the whole study period, whereas that of tobramycin showed more fluctuations (1-9%), reflecting however more local problems in some Intensive Care Units than a general trend. The MIC distributions of gentamicin and tobramycin were bimodal with one subpopulation with MICs over a broad from 0.12-4 mg/l and a very small subpopulation with MIC > 16 mg/l (figure 29). The MIC distribution of amikacin was unimodal over a broad range from 0.5 - > 16 mg/l. In general, MICs of tobramycin were two-fold lower than those of gentamicin and four-fold lower than those of amikacin. Tobramycin-resistant strains were also gentamicin-resistant, but not always amikacin-resistant. When using CLSI breakpoints instead of EUCAST, the resistance percentages of the aminoglycosides would have been 1-2% lower for Intensive Care Units.
Ciprofloxacin resistance showed a slowly increasing trend in Unselected Hospital Departments from 2% in 1998 to 6% in 2008 (figure 27). Ciprofloxacin resistance was higher in Intensive Care Units, the trend increased from 13% in 1998 to 20% in 2007. The resistance level Urology Services was already 18% in 1998 but the trend was decreasing to 13% in 2007. The levels of resistance to levofloxacin paralleled those of ciprofloxacin, but were mainly 2-3% higher. The use of EUCAST instead of CLSI breakpoints had influence on the levels of resistance for both levofloxacin and ciprofloxacin, the resistance trend for ciprofloxacin would have been from 7-13% instead of from13-20% in Intensive Care Units and around 10% in Urology Services without a visible decrease.

Summary – *Pseudomonas aeruginosa*
1. Using EUCAST breakpoints for resistance instead of CLSI breakpoints had impact on the resistance percentages to piperacillin, aminoglycosides and ciprofloxacin.
2. Increasing resistance to piperacillin, ceftazidime and ciprofloxacin in Intensive Care Units.
3. Decreasing resistance to ciprofloxacin in Urology Services.
4. Local problems with resistant circulating clones in a limited number of Intensive Care Units might have influenced the overall resistance level of piperacillin, meropenem, gentamicin and ceftazidime in a given year. This underlines the importance of local surveillance.

Enterococcus faecalis
Before 2002, no amoxicillin-resistant *E. faecalis* strains were found in Intensive Care Units and Urology Services. Starting in 2002 these strains spread slowly across the country: one Intensive Care Unit was positive in 2002, two in 2003 en 2004 and three in 2007. The resistance level increased from 4-10%. The resistance in Urology Services was found occasionally from 2002 onwards, fluctuating between 1-9%; the resistance level in Unselected Hospital Departments was 2% in 2008. Vancomycin resistance in Intensive Care Units was found in one centre in 2003 and in one in 2007; two Urology Services had vancomycin-resistant strains. Twelve from 13 vancomycin-resistant strains were also teicoplanin-resistant, which is evidence for clonal spread of a VanA gene positive strain. MICs for both drugs were >128 mg/l. Eight strains were co-resistant to amoxicillin. Resistance to amoxicillin is more frequent in *E. faecium*, but this species was not investigated.

Summary – *Enterococcus faecalis*
1. Amoxicillin resistance was spreading slowly and increasing.
2. Vancomycin and teicoplanin resistance was sporadic during the study period.

Staphylococcus aureus
In 2008, a total number of 2693 MRSA isolates were forwarded to the National Institute of Public Health and the Environment (RIVM) for typing, which is similar to the number received in 2007 (figure 30). The percentage of CC398 strains, as derived from spa-type, was 41% in 2008 (30% in 2007 as derived from smaI PFGE non-typeability, i.e. NT-MRSA). Most of the CC398 isolates were from people having close contacts with pigs and calves who were systematically screened at entry into hospitals as advised by the Dutch Working Party on Infection Prevention since the second half of 2006. According to electronic surveillance (ISIS-AR), 1.4% of the *S. aureus* strains isolated in The Netherlands in 2008, was MRSA, a 50% decrease compared to 2007. This decrease was probably due to a remake of the ISIS database comprising a change in the panel of participating laboratories and a more complete removal of isolates from MRSA screening. The actual incidence of MRSA isolates per province in The Netherlands is continuously reported at http://www.rivm.nl/mrsa.
The overall percentage of MRSA in Unselected Hospital Departments increased slowly from 0.5% in 1998 to 2% in 2008 (figure 31). Sporadically, MRSA strains were isolated from the Intensive Care Units (N = 7 from 1998-2007) and the Urology Services (N = 7 from 1998-2007). Four out of seven MRSA strains from Intensive Care Units were ciprofloxacin and clarithromycin resistant,

Download from SWAB.nl | 2026-11-12 14:20

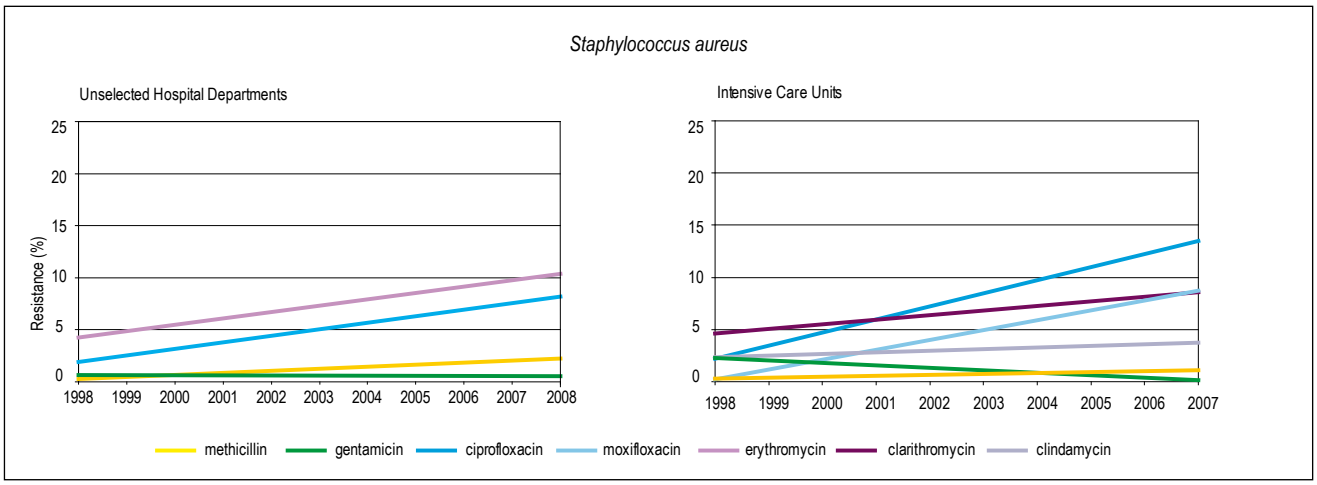
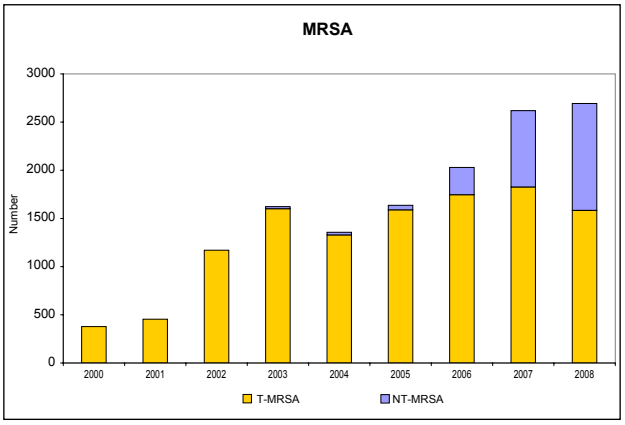


Figure 31. Trends in antibiotic resistance among clinical strains of *Staphylococcus aureus* from Unselected Hospital Departments and Intensive Care Units.

one was also gentamicin resistant.
Erythromycin resistance in Unselected Hospital Departments was slowly increasing to 10% in 2008 (figure 31). Clarithromycin resistance among strains from Intensive Care Units increased from 5% in 1998 to 9% in 2007; the resistance rate in Urology Services paralleled that of the Intensive Care Units. No data on clindamycin resistance in Unselected Hospital Departments were available from 1998-2007, it was 7% in 2008. Clindamycin resistance in Intensive Care Units fluctuated around 4% over the years without a shift or clear trend. Ciprofloxacin resistance rose among isolates from Unselected Hospital Departments from 2% in 1998 to 8% in 2008 (figure 31). Ciprofloxacin resistance in Intensive Care Units increased from 2% in 1998 to 14% in 2007. Moxifloxacin resistance followed that of ciprofloxacin resistance, although at a lower level (9% in 2007). Strains from Urology Services showed high resistance rates from 2003 on (30-40%), but the numbers of strains were very small (30 to 40 per year).
Gentamicin resistance fluctuated between 0.4% and 1% in Unselected Hospital Departments without a trend; it was higher in Intensive Care Units (1-4%) from 1998 to 2004 and not found thereafter. The use of EUCAST breakpoints had influence on the resistance level of gentamicin; when using CLSI breakpoints 1-2% resistance would have been recorded in 2003 and 2004 only.
Vancomycin resistance in Unselected Hospital Departments remained less than 0.1% during the whole study period and it was not found yearly. Vancomycin resistance was not recorded in the selected departments. Teicoplanin resistance was occasionally found in Intensive Care Units, at levels less than 0.1%.

Figure 30. Numbers and origin of MRSA in The Netherlands.



Summary – *Staphylococcus aureus*
1. Continuous low prevalence of MRSA in Unselected Hospital Departments.
2. Increase of resistance to macrolides and quinolones in Unselected Hospital Departments and Intensive Care Units.

Staphylococcus epidermidis
No differences in resistance percentages for all antibiotics tested could be found when applying EUCAST breakpoints for resistance instead of CLSI breakpoints.
Methicillin resistance (determined by oxacillin resistance) was frequently found among hospital isolates of *S. epidermidis*. Methicillin resistance in Unselected Hospital Departments increased from 41% in 1998 to 58% in 2008 (figure 32). Eighty percent of all strains from Intensive Care Units were methicillin-resistant. Methicillin-resistant strains were often co-resistant to

Download from SWAB.nl | 2026-11-12 14:20

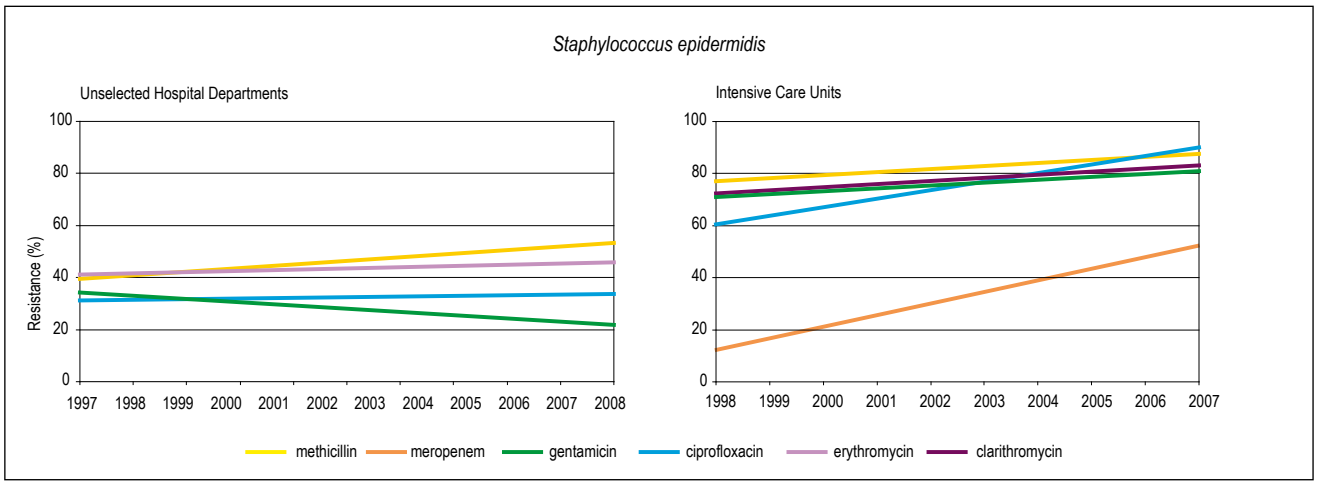
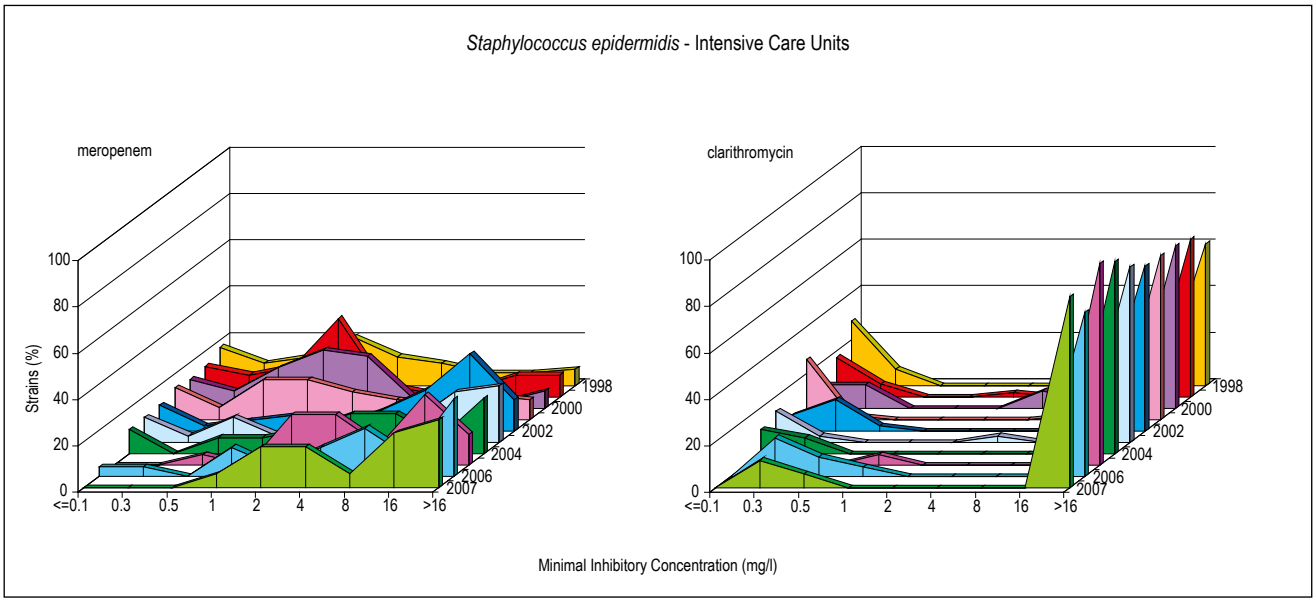


Figure 32. Trends in antibiotic resistance among clinical strains of *Staphylococcus epidermidis* from Unselected Hospital Departments and Intensive Care Units.

Figure 33. MIC distributions of meropenem and clarithromycin for *Staphylococcus epidermidis* from Intensive Care Units.



erythromycin, clarithromycin, gentamicin, ciprofloxacin and meropenem. The emergence of resistance to meropenem in Intensive Care Units was impressive, being less than 20% until 2001 increasing to 53% in 2007. The MIC distribution (figure 33) was more or less bimodal until 2005 with a small subpopulation of strains with MIC ≤ 0.25 mg/l and another subpopulation over a large range (MIC 1 - ≥16 mg/l) with the median at 2 mg/l. A clear shift to the right was observed from 2002 onwards with disappearance of the small susceptible subpopulation and appearance of a cluster of strains with MIC > 8 mg/l. Erythromycin resistance increased steadily in Unselected Hospital Departments from 40% in 1998 to 49% in 2008, clarithromycin resistance in Intensive Care Units was much higher and showed an increasing trend from 70% in 1998 to 80% from 2000 onwards. The MIC distribution was bimodal with a large cluster with MICs >16 mg/l and a very small cluster with MICs of 0.5 mg/l or less (figure 33). The peak of the susceptible cluster seemed to flatten and to move to higher MICs. Clindamycin resistance in Unselected Hospitals was 36% in 2008 compared to almost 90% among strains from Intensive Care Units in 2007 (figure 34). Gentamicin resistance in Unselected Hospital Departments decreased from 32% in 1998 to 21% in 2008. Gentamicin resistance in Intensive Care Units increased from 70% in 1998 to 80% in 2007. Ciprofloxacin resistance in Unselected Hospital Departments was stable at a 33% level during the whole study period, that in Intensive Care Units was much higher from the beginning (60%) and it increased to 90% in 2007.

Co-trimoxazole and rifampicin resistance was significantly higher among strains from Intensive Care

Download from SWAB.nl | 2026-11-12 14:20

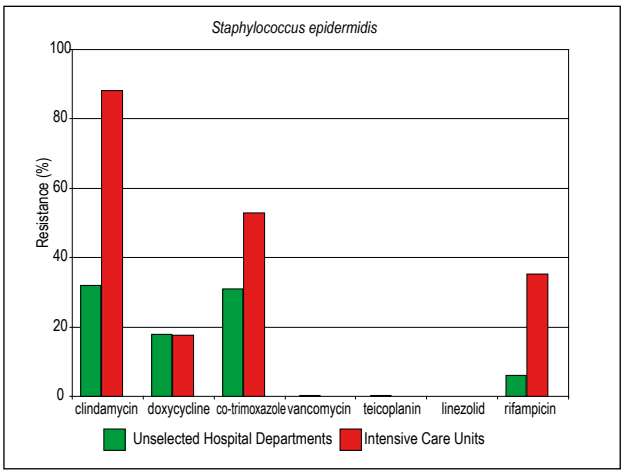


Figure 34. Resistance rates (%) for various antibiotics among clinical strains of *Staphylococcus epidermidis* from Unselected Hospital Departments (2008) and Intensive Care Units (2007).

Units compared to those from Unselected Hospital Departments, in contrast with doxycycline resistance which was 18% in all departments (figure 34).
Vancomycin resistant strains were reported occasionally in Unselected Hospital Departments and once in one Intensive Care Unit in 2002. The vancomycin resistant strain was also teicoplanin resistant (MIC 256 mg/l). Linezolid resistance was not recorded.
High resistance levels to many drugs among *S. epidermidis* from Intensive Care Units are common, apparently as a result of high selective pressure in these wards. Often these strains belong to specific populations circulating in Intensive Care Units and colonizing many patients. Such populations may serve as a reservoir for multiresistance with the risk of exchange of resistance factors to other micro-organisms in the commensal flora of patients and health care workers.

Summary – *Staphylococcus epidermidis*

1. Using EUCAST breakpoints for resistance instead of CLSI breakpoints had no impact on the resistance percentages to the antibiotics tested.
2. High resistance levels and multiresistance was common among strains from Intensive Care Units.
3. Increasing resistance to macrolides in Unselected Hospital Departments and Intensive Care Units.
4. Increasing resistance to meropenem, gentamicin and ciprofloxacin in Intensive Care Units.
5. Decreasing resistance to gentamicin in Unselected Hospital Departments.
6. Glycopeptide resistance was sporadic in all hospital departments.

Streptococcus pneumoniae

Streptococcus pneumoniae strains resistant to penicillin (MIC > 2 mg/l) are not often isolated in The Netherlands. In 2008, 1% of all pneumococci from Unselected Hospital Departments were resistant, whereas another 1% was categorized as intermediate (MIC 0.5-1.0 mg/l). Taking resistant and intermediate strains together over the years, a slight increase of resistant and intermediate strains was observed from 1% in 1998 to 2% in 2008 (figure 35). The resistance level and trend in Pulmonology Services were similar. The resistance to cefaclor increased to 13% in Pulmonology Services, that to cefuroxime was less than 3% during the whole study period; cefotaxime was the most active against *S. pneumoniae* in both Unselected Hospital Departments and Pulmonology Services with less than 1% resistance rate during the whole study period. The use of EUCAST breakpoints for resistance instead of CLSI criteria did not change the resistance rates.
Increasing resistance to macrolides among clinical isolates of *S. pneumoniae* from all departments was observed from 2000 onwards, resulting in resistance percentages of 10% for erythromycin in Unselected Hospitals in 2008. The resistance rates in Unselected Hospital Departments included intermediate and resistant strains. In 2008, resistant strains and intermediate ones were separated. When including only resistant strains, the resistance level to erythromycin in 2008 should have been 9% instead of 10%. Clarithromycin in Pulmonology Services was 9% in 2007.
Resistance rates of doxycycline in Unselected Hospitals included intermediate and resistant strains and increased slowly to 7% in 2008 with some fluctuations. When including only resistant strains the resistance level would have been 4% in 2008. The resistance level in Pulmonology Services (only resistant strains with MIC > 2 mg/l) was consistently higher during the whole study period and showed a decreasing trend from 14% in 1998 to 11% in 2007 (figure 35). If also intermediate strains were included, the resistance rate in 2007 would have been 12%. The difference in resistance levels between Unselected Hospital Departments and Pulmonology Services may reflect the frequent use of doxycycline in exacerbations in COPD patients frequently visiting the Pulmonology Services. The use of EUCAST breakpoints for resistance instead of CLSI criteria did affect the resistance rates of doxycycline (figure 35). When using the breakpoint for resistance recommended by CLSI (MIC > 4 mg/l) instead of that of EUCAST (MIC > 2 mg/l), the resistance rates should have been lower during the study period and not have decreased, but increased from 8% in 1998 to 11% in 2007. The MIC distributions (figure 36) showed a change from 2001 onwards. Until that time a large subpopulation with MIC < 0.25 mg/l and a small subpopulation over a broad range (MIC 1_16 mg/l) were observed. Strains in this area with MIC = 4 mg/l are recorded resistant according to EUCAST,

Download from SWAB.nl | 2026-11-12 14:20

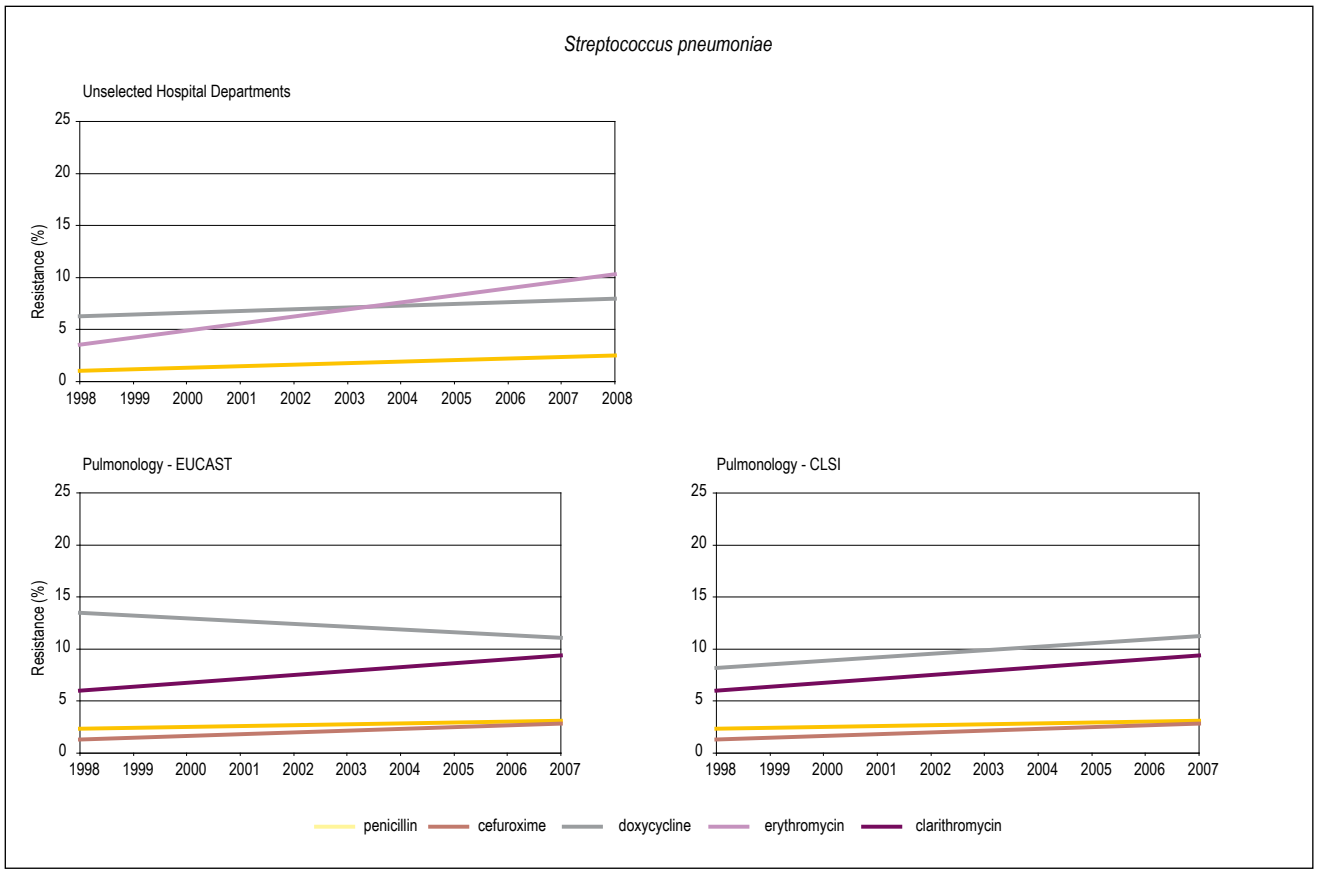
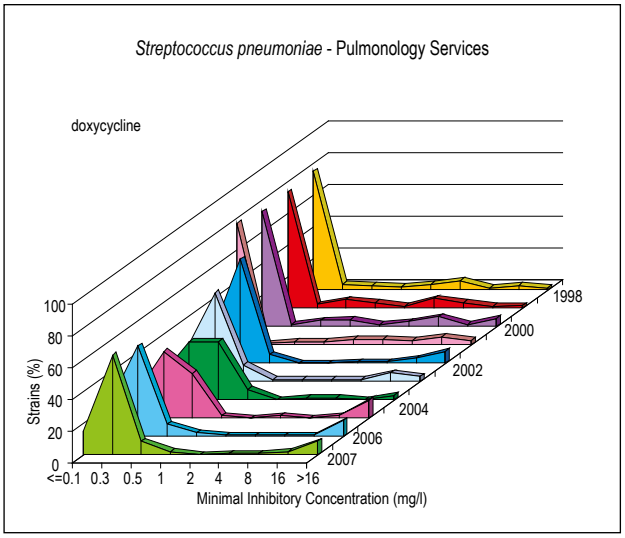


Figure 35. Trends in antibiotic resistance among clinical strains of *Streptococcus pneumoniae* from Unselected Hospital Departments and Pulmonology Services. Trends in Pulmonology Services were calculated according to the breakpoints for resistance recommended by both EUCAST and CLSI.

Figure 36. MIC distributions of doxycycline for *Streptococcus pneumoniae* from Pulmonology Services.



but not resistant according to CLSI, which may explain the different resistance rates. From 2002 onwards the distribution became bimodal with a small subpopulation with MIC ≥ 16 mg/l (resistant for both EUCAST and CLSI) and the intermediate subpopulation (resistant for EUCAST, but not for CLSI) disappeared, thus resulting in decreasing resistance levels by EUCAST and increasing resistant levels by CLSI.

Co-trimoxazole resistance was 17% in Unselected Hospital Departments in 2008, which was much higher than the resistance rate ever found in Pulmonology Services (2-6%). We have no explanation for this finding.

Ciprofloxacin resistance recorded in Unselected Hospital Departments fluctuated considerably over the years (4-24%). The overall trend showed a decrease from 22% in 1998 to 10% in 2007 (not shown). In 2008, a level of 37% resistance was recorded. Apparently, intermediate and resistant strains were included in the tests and it was unclear which breakpoints were used to determine the resistance rate. The breakpoint for susceptibility recommended by EUCAST is very low (MIC < 0.125 mg/l), which implies that many wild type *S. pneumoniae* strains (MIC 0.25-1 mg/l) are categorized as intermediate. The breakpoint for susceptibility recommended by CLSI is higher (MIC < 1 mg/l),

Download from SWAB.nl | 2026-11-12 14:20

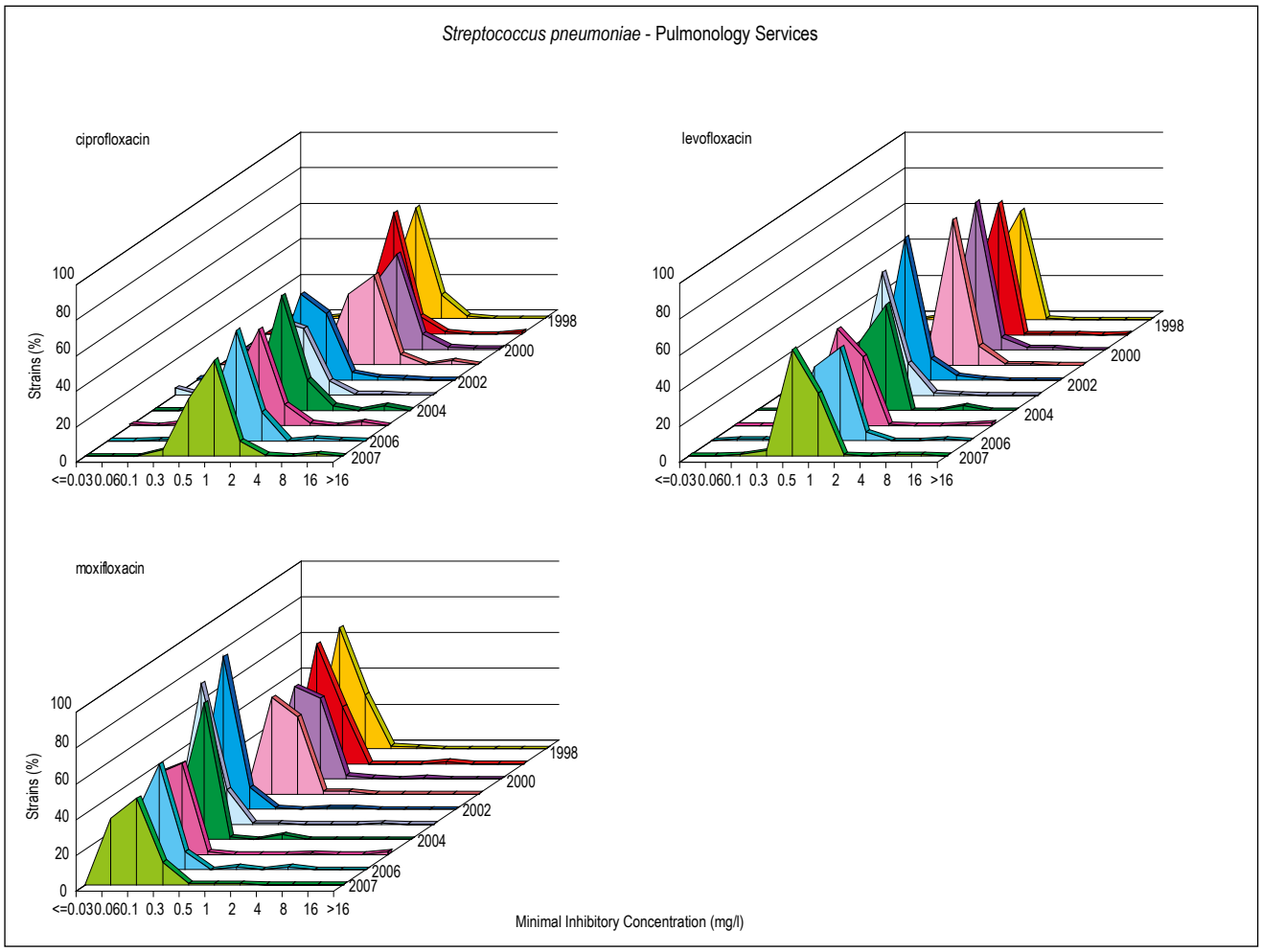


Figure 37. MIC distributions to quinolones for *Streptococcus pneumoniae* from Pulmonology Services.

so dependant on the breakpoints used, the resistance percentages may vary considerably. When including only resistant strains (MIC > 2 mg/l, the breakpoint for resistance recommended by both EUCAST and CLSI) from Unselected Hospital Departments, the resistance level for ciprofloxacin should have been 11% in 2008. Ciprofloxacin resistance rates in Pulmonology Services also showed fluctuations, the overall trend decreased from 6% in 1998 to 2% in 2007. Levofloxacin- and moxifloxacin resistance rates in 2007 were 2% and 1% respectively. Resistance percentages are not informative on changes and shifts in susceptibility patters. MIC distributions of both ciprofloxacin and levofloxacin were comparable and showed that 90% of the strains had MICs 0.5-1 mg/l during the whole study period, without significant changes over the years (figure 37). The MIC distribution of moxifloxacin showed a unimodal distribution with 90% of MICs 0.06-0.12 mg/l.

Summary – *Streptococcus pneumoniae*

1. Use of EUCAST breakpoints instead of CLSI breakpoints for resistance had impact on the resistance percentages of doxycycline and quinolones.
2. Penicillin resistance remained low (2% or less).
3. Increase of resistance to macrolides in all departments.
4. Consistent higher resistance level to doxycycline in Pulmonology Departments compared to that in Unselected Hospital Departments.
5. Decreasing resistance to doxycycline in Pulmonology Services.
6. Decreasing resistance to ciprofloxacin in all hospital departments.

Download from SWAB.nl | 2026-11-12 14:20

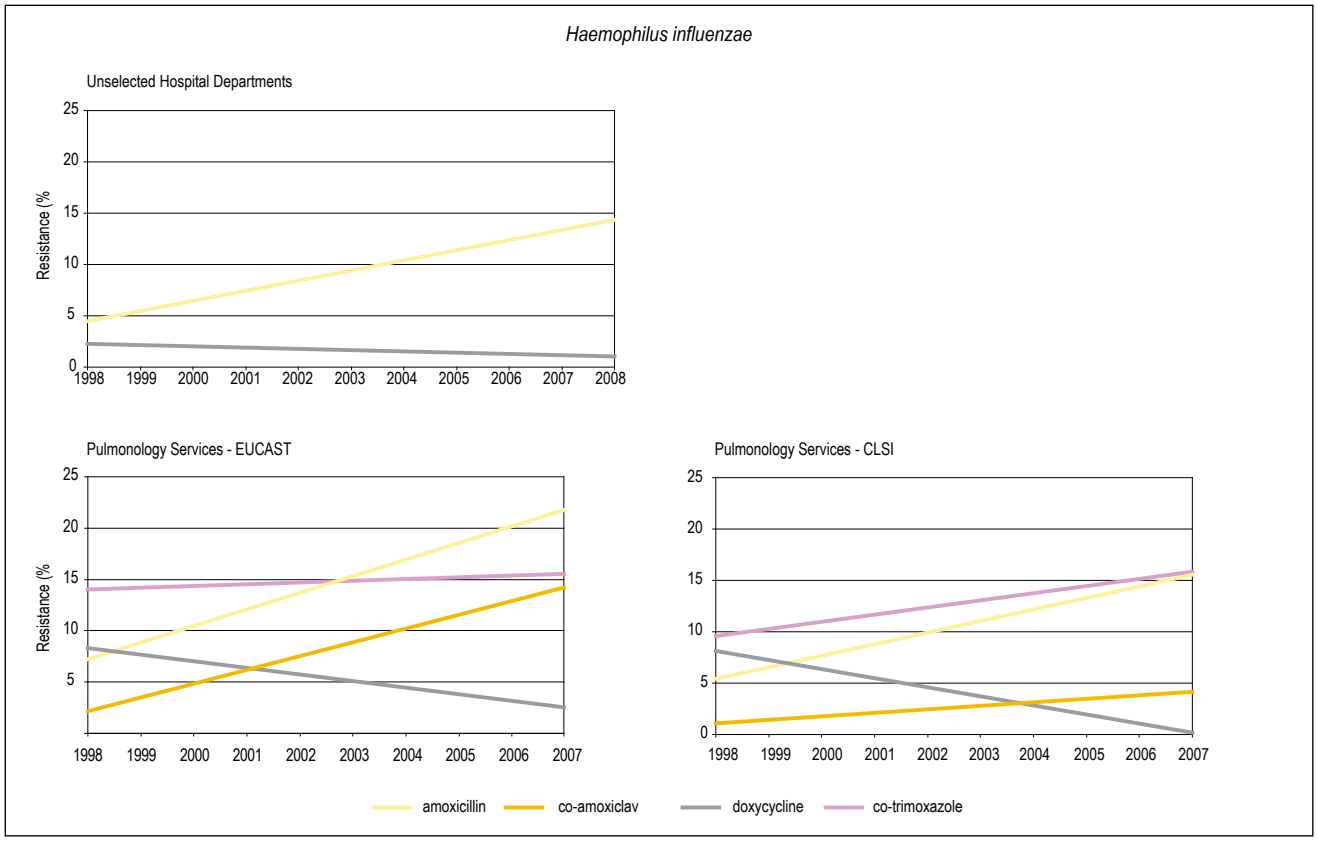
Haemophilus influenzae

Amoxicillin resistance among *H. influenzae* from Unselected Hospital Departments showed an increasing trend to 15% in 2008 (figure 38). Co-amoxiclav was not tested until 2007, it was 3% in 2008, which implied that 85% of amoxicillin-resistance was based on beta-lactamase production. Amoxicillin resistance in Pulmonology Services was consistently higher and increased from 8% in 1998 to 21% in 2007, whereas co-amoxiclav resistance increased from 2% in 1998 to 14% in 2007. The resistance levels of both amoxicillin and co-amoxiclav would have been significantly lower with use of CLSI breakpoints for resistance (MIC > 2mg/l) instead of EUCAST breakpoints breakpoints for resistance (MIC > 1 mg/l): 16% resistance to amoxicillin and 4% to co-amoxiclav in 2007, respectively (figure 38). This is quite understandable when studying the MIC distributions (figure 39) which showed a trend to bimodal distribution for amoxicillin with a number of strains with MIC= 2 mg/l, resistant according to EUCAST criteria but still susceptible according to CLSI criteria. The same can be observed for co-amoxiclav. Furthermore, the distributions of amoxicillin and co-amoxiclav suggested a broadening and a shift in 2003 with more strains in the MIC range 1-4 mg/l. The increasing amoxicillin and co-amoxiclav resistance is a matter of concern.

Macrolide resistance in *H. influenzae* is difficult to determine because of the large interval between the breakpoints for susceptibility and resistance indicated by EUCAST. The resistance rate for erythromycin in strains from Unselected Hospital Departments included intermediate and resistant strains and it increased from 69% in 1998 to 98% in 2008 (not shown). Clarithromycin resistance in Unselected Hospital Departments was 19% in 2008. This is quite in concordance with the findings among strains from Pulmonology Services, where clarithromycin resistance MIC > 32 mg/l) increased with fluctuations from 3% in 1998 to 20% in 2007. When using the CLSI breakpoint for resistance (MIC > 1 mg/l) instead of the EUCAST breakpoint for resistance (MIC > 32 mg/l), the resistance level of clarithromycin should have been 99% in 2007. This means that about 80% of H. influenzae strains had MICs in the area from 2-16 mg/l, categorized as intermediate susceptible.

Low resistance rates (1-2%) were found for doxycycline among *H. influenzae* isolates from Unselected Hospital Departments (figure 38). The resistance rates in Pulmonology Services were higher from the beginning (9%) and decreased to 2% in 2008, a level similar to that in Unselected Hospital Departments. Less use of doxycycline by increasing use of quinolones and macrolides in respiratory tract infections may be an

Figure 38. Trends in antibiotic resistance among clinical strains of *Haemophilus influenzae* from Unselected Hospital Departments and Pulmonology Services. Trends in Pulmonology Services were calculated according to the breakpoints for resistance recommended by both EUCAST and CLSI.



Download from SWAB.nl | 2026-11-12 14:20

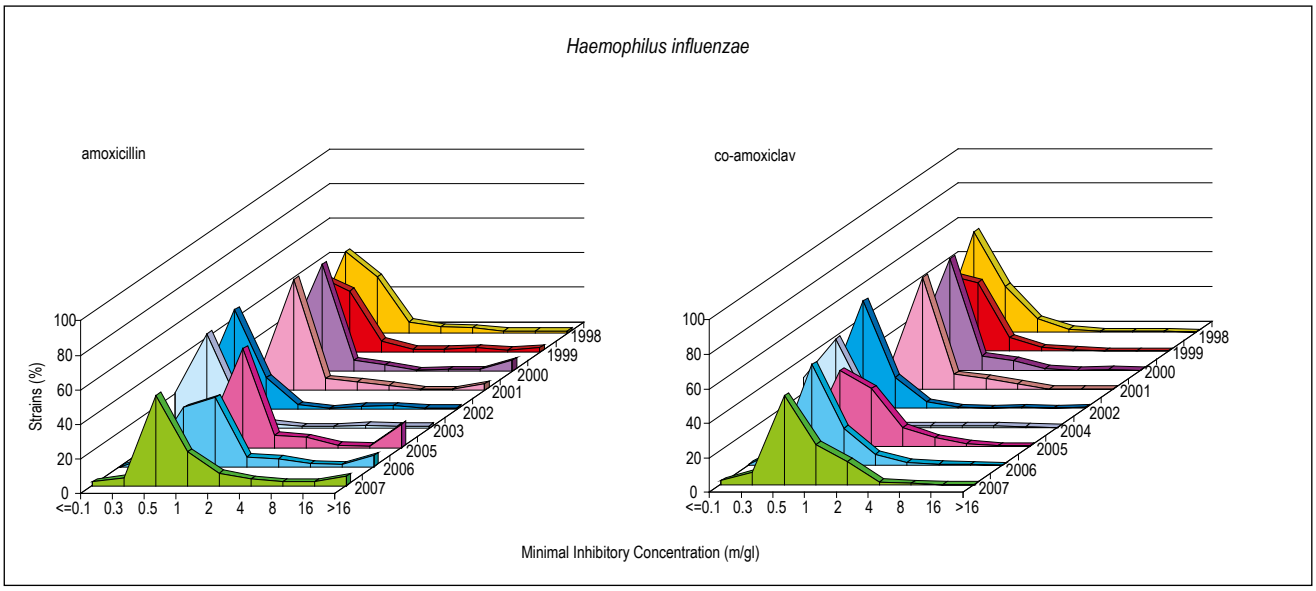


Figure 39. MIC distributions of amoxicillin and co-amoxiclav for *Haemophilus influenzae* from Pulmonology Services.

explanation for decreased resistance rate. Use of the breakpoint for resistance of CLSI (MIC > 4 mg/l) instead that of EUCAST (MIC > 2 mg/l) had no significant effect on the resistance levels (figure 38).
A matter of concern is the high resistance to co-trimoxazole, which is one of the drugs used in COPD exacerbations. The resistance level in Pulmonology Services fluctuated around 15% over the years without a visible trend, but this is too high for use of co-trimoxazole as empiric therapy. The resistance level in Unselected Hospitals in 2008 (17%) was comparable to that of Pulmonology Services in 2007. Use of the EUCAST breakpoint for resistance (MIC > 1 mg/l) had effect on the resistance levels for co-trimoxazole (figure 38); the resistance trend should have increased from 9% in 1998 to 16% in 2007, when using the CLSI breakpoint for resistance (MIC > 2 mg/l).
Ciprofloxacin resistance (MIC > 0.5 mg/l) occurred sporadically in Unselected Hospital Departments and Pulmonology Services.

Summary – *Haemophilus influenzae*

1. Using EUCAST breakpoints for resistance instead of CLSI breakpoints had impact on the resistance percentages to beta-lactams, co-trimoxazole and macrolides.
2. Increasing resistance to amoxicillin and co-amoxiclav in Unselected Hospital Departments and Pulmonology Services.
3. High resistance (15-17%) to co-trimoxazole in Unselected Hospital Departments and Pulmonology Services.
4. Decreasing resistance to doxycycline in Pulmonology Services.

Moraxella catarrhalis

Amoxicillin resistance among *M. catarrhalis* isolated in Unselected Hospital Departments was around 80% during the whole study period. The resistance in Pulmonology Services fluctuated around 45% over the whole study period. The difference in resistance levels between strains from Unselected Hospital Departments and those of Pulmonology Services is unclear. The resistance was completely due to beta-lactamase since resistance to co-amoxiclav did not occur.
Cephalosporin resistance varied in Pulmonology Services. Resistance to cefaclor was 8% in 1998 and decreased to 1% or less in 2007. Cefuroxime resistance was 0-,5% over the years, apparently without a clear trend, but when looking at the MIC distribution a clear shift was observed from 2004 on (figure 40). In 2002 and 2003 the MIC distributions were unimodal over a broad range from < 0.03-0.5 mg/l; thereafter the whole population moved to the right with most MICs 0.5-4 mg/l and a clear peak of strains with MIC = 2 mg/l. This is the breakpoint of intermediate resistance when using EUCAST breakpoints. The MIC distributions for cefotaxime showed a bimodal shape with two subpopulations, one in the range of MICs < 0.03-0.12 mg/l and one in the range of MICs 0.5-1 mg/l. The latter subpopulation should be categorized resistant when using EUCAST breakpoints for resistance (MIC > 0.12 mg/l) since this Committee stated that the occurrence of strains with MIC > 0.12 mg/l is very rare. This was not our experience as 53% of all Moraxella strains tested had MIC > 0.12 mg/l for cefotaxime. This should imply a resistance rate of 60% to cefotaxime in 2007. When using CLSI breakpoints (MIC > 2 mg/l), all these strains should be recorded susceptible and the resistance percentage should have been 0% during all years. The low breakpoint of resistance for cefotaxime advised

Download from SWAB.nl | 2026-11-12 14:20

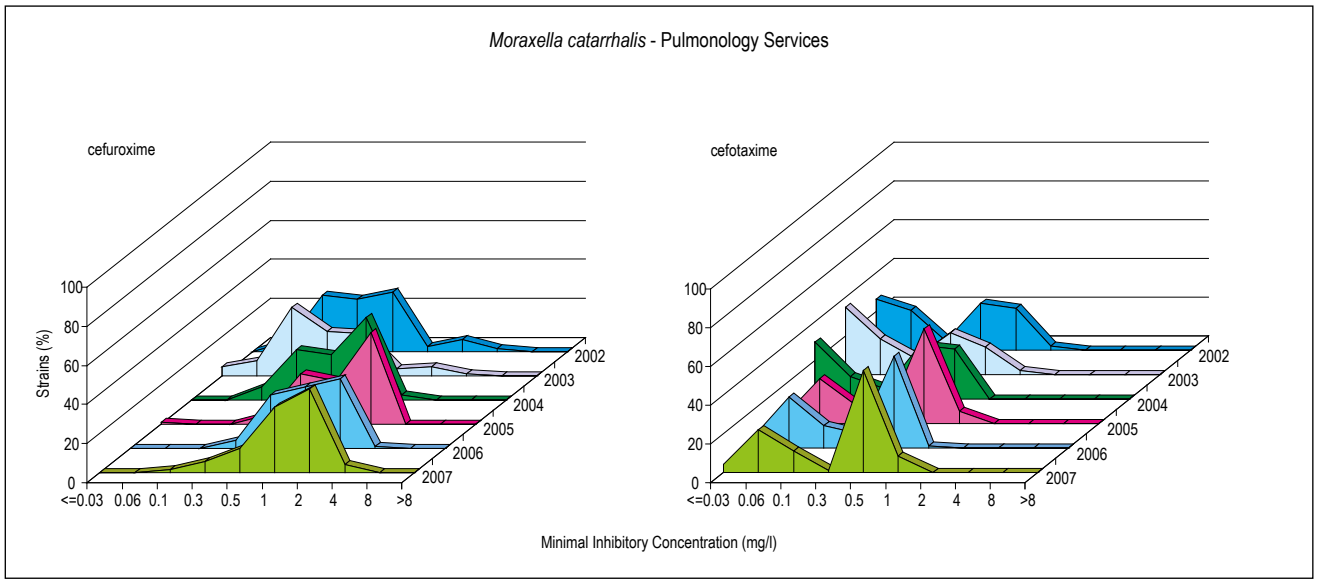


Figure 40. MIC distributions of cefuroxime and cefotaxime for *Moraxella catarrhalis* from Pulmonology Services.

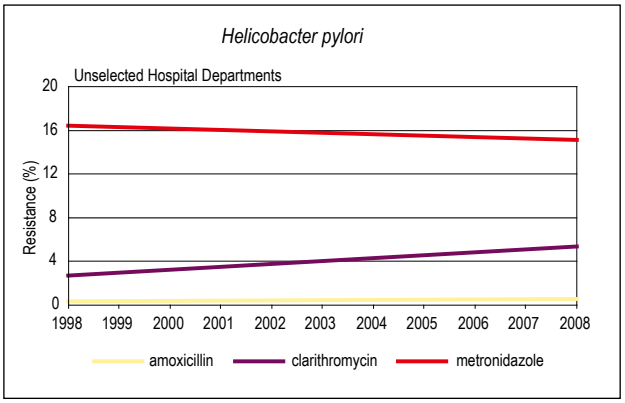
by EUCAST may need reconsideration in view of this finding.
Resistance to erythromycin in Unselected Hospital Departments almost doubled from 4% in 1996 to 7% in 2007. Clarithromycin resistance in Pulmonology Services was 1-5% and did not show any trend of development of resistance. The lower resistance rate of clarithromycin compared to erythromycin may be explained by a higher intrinsic activity of clarithromycin towards *M. catarrhalis*: MICs of clarithromycin were 2-4 fold lower than those of erythromycin, which may have resulted in different resistance percentages at the same breakpoint.
Ciprofloxacin resistance was occasionally found.
Resistance to doxycycline fluctuated between 2-4% in Unselected Hospital Departments during the whole study period and was 4-8% in Pulmonology Services until 2001. Thereafter no resistance was found except in 2005 (1% resistance).

Summary – *Moraxella catarrhalis*
Amoxicillin resistance is completely due to production of beta-lactamase.
Increase of macrolide resistance in Unselected Hospital Departments.
The low breakpoint for resistance to cefotaxime recommended by EUCAST seems not realistic.

Helicobacter pylori

Amoxicillin resistance among *H. pylori* from Unselected Hospital Departments was less than 3% over the years (figure 41). Clarithromycin resistance was 1-5% (mean 4%) until 2007. In 2008 the resistance percentage was 8%, but the number of strains isolated was very low compared to the years before. Doxycycline resistance was sporadic until 2004 and not tested thereafter.
Metronidazole resistance was stable over the years with some fluctuations (12-17% resistance); in 2008 a resistance percentage of 14% was found.

Figure 41. Trends in antibiotic resistance among clinical strains of *Helicobacter pylori* from Unselected Hospital Departments.



Download from SWAB.nl | 2026-11-12 14:20

Surveillance studies published in the international peer-reviewed literature containing quantitative susceptibility data of bacterial pathogens isolated in The Netherlands

Apart from the surveillance data presented in NethMap on the basis of the surveillance system developed by SWAB, several individual studies by other authors have reported on the occurrence of antimicrobial resistances among various bacterial species in The Netherlands. These studies were selected for inclusion in NethMap if they met the following criteria: (1) all studies reported on resistance rates based on the measurements of MICs, i.e. quantitative susceptibility tests were performed on all strains; (2) all strains were collected from patients in multiple centres throughout The Netherlands and (3) the studies were reported in peer-reviewed journals, listed in the Medline database. Individually, and taken together these studies provide further insight into the prevalence and emergence of antimicrobial resistance among medically important micro-organisms in The Netherlands.
In addition to the list of studies readers are helped by a cross table that reveals the combinations of "bugs & drugs" for which data were reported in each of the listed studies.

1. Buirma RJA, Horrevorts AM, Wagenvoort JHT. Incidence of multiresistant Gram-negative isolates in eight Dutch hospitals. Scand J Infect Dis (suppl) 1991; 78: 35-44.
2. Bongaerts GPA, Hoogkamp-Korstanje JAA. In vitro activities of BAY Y3118, ciprofloxacin, ofloxacin and fleroxacin against Gram-positive and Gram-negative pathogens from respiratory tract and soft tissue infections. Antimicrob Agents Chemother 1993; 37: 2017-2019.
3. Stobbering EE, Maclaren DM et al. Comparative in-vitro activity of piperacillin-tazobactam against recent clinical isolates, a Dutch national multicentre study. J Antimicrob Chemother 1994; 34: 777-783.
4. Enting RH, Spanjaard L et al. Antimicrobial susceptibility of *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae* isolates causing meningitis in the Netherlands 1993-1994. J Antimicrob Chemother 1996; 38:777-786.
5. Zwet AA van, Boer WA de et al. Prevalence of primary *Helicobacter pylori* resistance to metronidazole and clarithromycin in The Netherlands. Eur J Clin Microbiol Infect Dis 1996; 15: 861-864.
6. Beek D van de, Hensen EF, et al. Meropenem susceptibility of *Neisseria meningitidis* and *Streptococcus pneumoniae* from meningitis patients in The Netherlands. J Antimicrob Chemother 1997; 40: 895-897.
7. Endtz HP, Dijk WC van, Verbrugh HA et al. Comparative in vitro activity of meropenem against selected pathogens from hospitalized patients in The Netherlands. MASTIN Study Group. J Antimicrob Chemother 1997 Feb; 39(2): 149-56
8. Endtz HP, Mouton JW et al. Comparative in vitro activities of trovafloxacin (CP-99,219) against 445 gram-positive isolates from patients with endocarditis and those with other bloodstream infections. Antimicrob Agents Chemother 1997; 41: 1146- 1149.
9. Hoogkamp-Korstanje JAA (1997) In-vitro activities of ciprofloxacin, levofloxacin, lomefloxacin, ofloxacin, pefloxacin, sparfloxacin and trovafloxacin against Gram-positive and Gram-negative pathogens from respiratory tract infections. J Antimicrob Chemoth 40: 427-431.
10. Hoogkamp-Korstanje JAA, Dirks-Go SIS, et al. Multicentre in-vitro evaluation of the susceptibility of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. J Antimicrob Chemother 1997; 39: 411-414.
11. Mouton JW, Endtz HP et al. In-vitro activity of quinupristin/dalfopristin compared with other widely used antibiotics against strains isolated from patients with endocarditis. J Antimicrob Chemother 1997; 39 Suppl A, 75-80.
12. Schouten MA, Hoogkamp-Korstanje M. Comparative in-vitro activities of quinupristin-dalfopristin against gram-positive bloodstream isolates. J Antimicrob Chemother 1997; 40: 213-219.
13. Wouden EJ van der, Zwet AA van et al. Rapid increase in the prevalence of metronidazole-resistant *Helicobacter pylori* in the Netherlands. Emerg Infect Dis 1997; 3 (3) 1-7.
14. Hoogkamp-Korstanje JAA, Verduyn-Lunel F, Meis, JFGM (1998) Cefpirome: epidemiological survey in intensive care units and hematological units in The Netherlands. The Dutch Study Group. Diagn Micr Infec Dis 31: 489-491.
15. Debets-Ossenkopp YJ, Herscheid AJ et al. Prevalence of *Helicobacter pylori* resistance to metronidazole, clarithromycin, amoxicillin, tetracycline and trovafloxacin in The Netherlands. J Antimicrob Chemother 1999; 43, 511-515.
16. Schouten MA, Voss A, Hoogkamp-Korstanje JAA. Antimicrobial susceptibility patterns of enterococci causing infections in Europe. Antimicrob Agents Chemother 1999; 37: 2542-2546.
17. Stobberingh EE, Arends J, Hoogkamp-Korstanje JAA, Goessens WHF, Visser MR, Buiting AGM, Debets-Ossenkop YJ, Ketel RJ van, Ogtrop ML van, Sabbe LJM, Voorn GP, Winter HLJ, Zeijl JH van (1999) Occurence of Extended-Spectrum Betalactamases (ESBL) in Dutch Hospitals. Infection 27(6): 348-354.
18. Hoogkamp-Korstanje JAA, Roelofs-Willemse J (2000) Comparative in-vitro activity of moxifloxacin against Gram-positive clinical isolates J Antimicrob Chemother 45: 31-39.
19. Mouton JW, Jansz AR. The DUEL study: A multicenter in vitro evaluation of linezolid compared with other antibiotics in the Netherlands. Clin Microbiol Infect 2001; 7: 486-491.
20. Bruinsma N, Filius PGM, De Smet PAGM, Degener J, Endtz Ph, Van den Bogaard AE, Stobberingh EE. Antibiotic Usage and Resistance in Different Regions of the Dutch Community. Microb Drug Resist. 2002, 8(3): 209-14.
21. Bruinsma N, Filius PM, van den Bogaard AE, Nys S, Degener J, Endtz HP, Stobberingh EE. Hospitalization, a risk factor for antibiotic-resistant *Escherichia coli* in the community? J Antimicrob Chemother. 2003;51(4):1029-32.
22. Hoogkamp-Korstanje JAA, Roelofs-Willemse J and the Susceptibility Surveillance Study Group. Antimicrobial resistance in Gram-negative bacteria from Intensive Care Units and Urology

Download from SWAB.nl | 2026-11-12 14:20

Services. A nationwide study in The Netherlands 1995-2000. Int J Antimicrob Ag 2003; 21: 547-556.
23. Loffeld RJ, Fijen CA. Antibiotic resistance of *Helicobacter pylori*: a cross-sectional study in consecutive patients, and relation to ethnicity. Clin Microbiol Infect 2003; 9: 600-4.
24. Bouchillon SK, Johnson BM, Hoban DJ, Johnson JL, Dowzicky MJ, Wu DH, Visalli MA Bradford PA Determining incidence of extended spectrum β-lactamase producing *Enterobacteriaceae*, vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* in 38 centres from 17 countries: the PEARLS study 2001–2002. Int J Antimicrob Agents 2004; 24: 119-24.
25. Nys S, Okeke IN, Kariuki S, Dinant GJ, Driessen C, Stobberingh EE. Antibiotic resistance of faecal *Escherichia coli* from healthy volunteers from eight developing countries. J Antimicrob Chemother. 2004;54(5): 952-5.
26. Tiemersma EW, Bronzwaer SL, Lyytikainen O, Degener JE, Schrijnemakers P, Bruinsma N, Monen J, Witte W, Grundman H, EARSS participants. methicillin-resistant *Staphylococcus aureus* in Europe, 1999-2002. Emerg Infect Dis 2004; 10: 1627-34..
27. Neeleman C, de Valk JA, Klaasen CH, Meijers S, Mouton JW. In vitro susceptibility and molecular characterisation of macrolide resistance mechanisms among *Streptococcus pneumoniae* isolates in The Netherlands: the DUEL 2 study. Clin Microbiol Infect 2005; 11: 312-8.
28. Wertheim HF, Vos MC, Boelens HA, Voss A, Vandenbroucke-Grauls CM, Meester MH, Kluytmans JA, van Keulen PH, Verbrugh HA. Low prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) at hospital admission in the Netherlands: the value of search and destroy and restrictive antibiotic use. J Hosp Infect 2004; 56: 321-5.
29. Nys S, Bruinsma N, Filius PM, van den Bogaard AE, Hoffman L, Terporten PH, Wildeboer-Veloo AC, Degener J, Endtz HP, Stobberingh EE. Effect of hospitalization on the antibiotic resistance of fecal *Enterococcus faecalis* of surgical patients over time. Microb Drug Resist. 2005 11(2):154-8.
30. Nys S, Tjhie JH, Bartelds AI, Heijnen ML, Peeters MF, Stobberingh EE. Erythromycin resistance in the commensal throat flora of patients visiting the general practitioner: a reservoir for resistance genes for potential pathogenic bacteria. Int J Antimicrob Agents. 2005; 26(2):133-7.
31. Al Naiemi N, Bart A, de Jong MD, Vandenbroucke-Grauls CM, Rietra PJ, Debets-Ossenkopp YJ, Wever PC, Spanjaard L, Bos AJ, Duim B. Widely distrinuted and predominant CTX-M extended spectrum beta-lactamases in Amsterdam. J Clin Microbiol 2006; 44 (8): 3012-4.
32. Nys S, van Merode T, Bartelds AIM, Stobberingh EE. Antibiotic treatment and resistance of unselected uropathogens in the elderly. Int J Antimicrob Agents 2006; 27: 236-41.
33. De Backer D, Christiaens T, Heytens S, Sutter A de, Stobberingh EE, Verschraegen G. Evolution of bacterial susceptibility pattern of *Escherichia coli* in uncomplicated urinary tract infections in a country with high antibiotic consumption: a comparison of two surveys with a 10-year interval. J Antimicrob Chemother 2008; 62: 364-68.
34. Muller AE, Valkenburg-van den Berg AW, Kreft D, Oostvogel PM, Sprij AJ, van Belkum A. Low rate of carriage of macrolide-resistant group B streptococci in pregnant women in The Netherlands. Eur J Obstet Gynaecol Reprod Biol 2008; 137: 17-20.
35. Nys S, Terporten P, Hoogkamp-Korstanje JAA, Stobberingh E. Trends in antimicrobial susceptibility of *Escherichia coli* isolates from the Urology Services in The Netherlands (1998-2005). J Antimicrob Chemother 2008; 62: 126-32.
36. Oudhuis GJ, Verbon A, Hoogkamp-Korstanje JAA, Stobberingh EE and The Susceptibility Surveillance Study Group. Antimicrobial resistance in *Escherichia coli* and *Pseudomonas aeruginosa* from Intensive Care Units in The Netherlands 1998-2005. Int J Antimicrob Agents 2008; 31:58-63.
37. Belkum A van, Melles DC, Peeters JK, van Leeuwen WB, van Duijkeren E, Huijsdens XW, Spalburg E, de Neeling AJ, Verbrugh HA, Dutch Working Party on Surveillance and Research of MRSA-SOM. Methicillin-resistant and -susceptible *Staphylococcus aureus* sequence type 398 in pigs and humans. Emerg Infect Dis 2008; 14(3): 479-83.
38. Prins JM, Degener JE, de Neeling AJ, Gyssens IC; SWAB Board. Experiences with the Dutch Working Party on antibiotic policy (SWAB). Euro Surveill. 2008; 13: 46.
39. Sande-Bruinsma N van de, Grundmann H, Verloo D, Tiemersma E, Monen J, Goossens H, Ferech M; European Antimicrobial Resistance Surveillance System Group; European Surveillance of Antimicrobial Consumption Project Group. Antimicrobial drug use and resistance in Europe. Emerg Infect Dis. 2008; 14:1722-30.
40. Deurenberg RH, Nulens E, Valvatne H, Sebastian S, Driessen C, Craeghs J, Brauwer E de, Heising B, Kraat YJ, Riebe J, Stals FS, Trienekens ThA, Scheres J, Friedrich AW, Tiel FH van, Beisser PS, Stobberingh EE. Cross-border dissemination of methicillin-resistant *Staphylococcus aureus*, Euregio Meuse-Rhin region. Emerg Infect Dis 2009, in press.
41. Deurenberg RH, Stobberingh EE. The molecular evolution of hospital- and community-associated methicillin-resistant *Staphylococcus aureus*. Curr Mol Med 2009; 9: 100-15.

Download from SWAB.nl | 2026-11-12 14:20

Table 1. Crosstable of combinations of species of bacteria and antibiotics for which MIC data are presented in the individual studies listed above.

	Staphylo cocci	Strepto cocci	Pneumo cocci	Enterococci	Enterobacteriaceae	Non-ferm Gram-bacteria	Haemphilus influenzae	Helicobacter pylori	Meningococci
Penicillin	7,8,11	8,11	4,6,7	7					4,6
Oxacillin	7								
Methicillin	3,40,41								
Flucloxacillin	8,11								
Ampicilin				3	1,25,33	1	4		
Amoxicillin		8,11	7	7,8,11,16,20,29	20,21,22,32,35,36			15	
Co-amoxiclav			10		1,7, 7,22,32,33,35,36	1,7	7		
Piperacillin	3			3	1,3,17,35,36	1,3,36			
Piperacillin/ tazobactam	3,7,		7	3,7	1,3,17,35,36	1,3,36	7		
Ticarcillin/ clavulanate	3			3	1,3,7	1,3,7	7		
Mezlocillin					1	1			
Cefaclor					37				
Cefazolin					1,20,21,25	1			
Cefoxitin					17				
Cefuroxime	11	11			1,7,36	1,7	7		
Ceftriaxone			4,6		1	1	4		4,6
Cefotaxime		11			1,7,17,31,36	1,7,32	2		
Ceftazidime					1,3,7,17,22,36	1,3,7,22,36	2		
Cefpirome				16	17				
Cefepime					17				
Cefixime					37				
Ceftibuten					37				
Aztreonam					1	1			
Imipenem	3,7,12	12	7,12	3,7, 2,16	1,3, 7,22	1,3,7,22,36	2		
Meropenem	7,12	12	7,12	7,12,16	7,17	7,36	7		
Vancomycin	7,8,11,12	8,11,12	7,12	7,8,11,12,16,20,29					
Teicoplanin	8,11,12	8,11,12	12	8,11,12,16					
Linezolid	19	19	19						
Gentamicin	3,7		7	7,11,16, 20,29	1,3,4,7,17,22,20,21,25,36	1,3,7,22,36	7		
Tobramycin					1,17	1,36			
Netilmicin					17				
Amikacin	3				1,3,17	1,3,36			
Norfloxacin					22,32,35,33	22			
Ciprofloxacin	2,3,7,8,12	2,8,12	2,7,10,12,	2,3,8,7,12, 16,20,29	1,2,3,7,22,20,21,25,35,36	1,2,3,7,22,36	2,7,10		
Ofloxacin	2,8	2,8	2	2,8,16	2,17	2	2		
Levofloxacin					35				
Trovafloxacin	8	8		8,16				15	
Sparfloxacin	8,12	8,12	10,12	8,12,16			10		
Pefloxacin	8	8		8					
Moxifloxacin				16	35				
Clindamycin	7,11,12	11	7	7,11					
Erythromycin	7,11,12	11,12,30	7,12	2,7,11,12, 20,29					
Clarithromycin	11	11,12,34	10,12	11,12			10	5,15	
Tetracyclin			20,29	20,29	20,21,25			15	
Minocyclin				11					
Chloramphenicol			4,6	16	20,25		4		4,6
Quinupristin/ dalfopristin	11,12	11,12	12	2,11,12					
Rifampicin	11,12	12	12	12					4,6
Metronidazole								5,13,15	
Trimethoprim					20,21,22, 25.32,33,35				
Co-trimoxazole					22,32,35				
Nitrofurantoin					20,22, 32,33,35				

Numbers correspond with referencenumbers listed above this crosstable .

Download from SWAB.nl | 2026-11-12 14:20

5. Resistance to influenza antiviral drugs

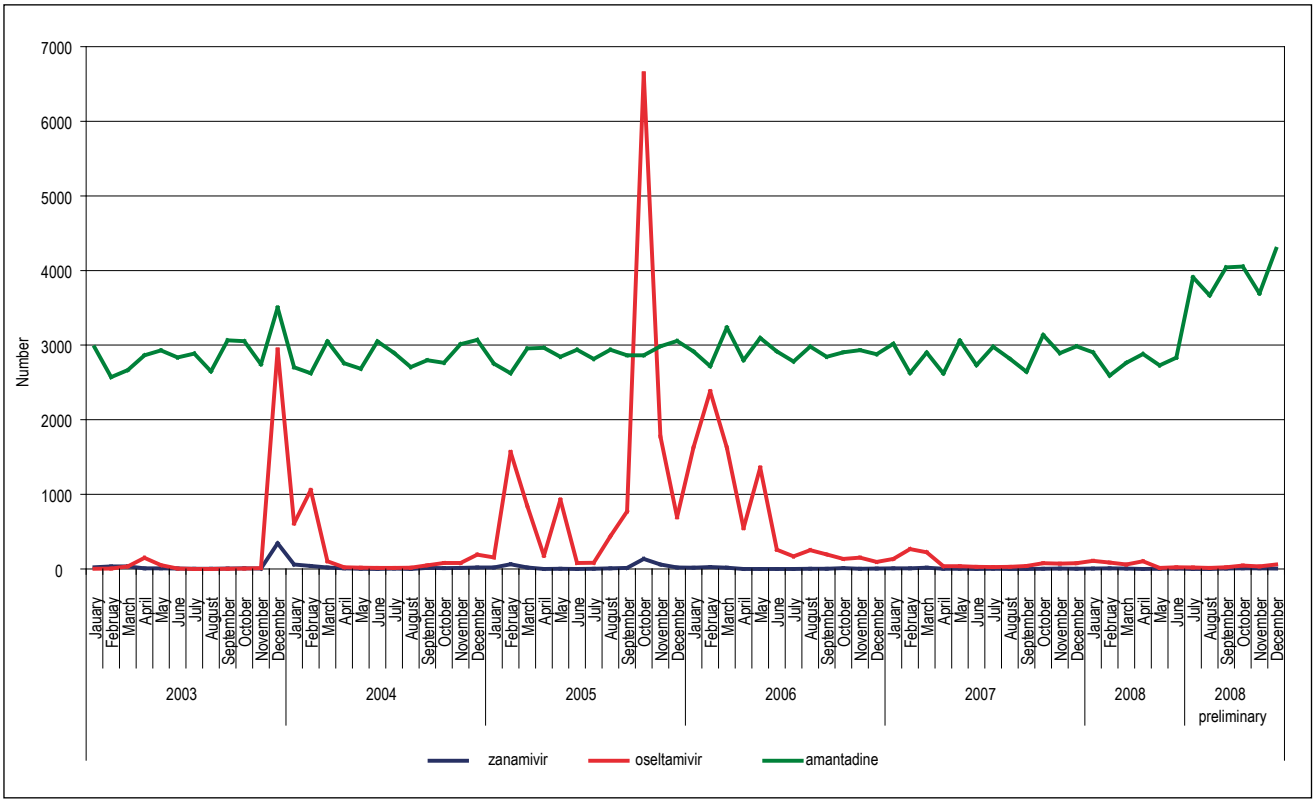
Adam Meijer and Marcel Jonges
National Institute for Public Health and the Environment, Centre for Infectious Disease Control, Bilthoven, The Netherlands

Infection by influenza A(H1N1), A(H3N2) or B viruses, results in substantial morbidity and excess mortality each year. Vaccination against seasonal influenza is the key control measure used in The Netherlands and Europe to minimize morbidity and mortality, especially in the risk groups for development of complications upon influenza virus infection. However, antigenic mismatch between vaccine components and circulating viruses does occur every few years requiring the vaccine to be reformulated. This together with sub-optimal vaccine uptake in recommended patient groups, non-responders to vaccination and waning immunity during the season provides the rationale for the use of antiviral drugs in the prophylaxis and treatment of influenza in special circumstances (1, 2).

Prescriptions of influenza antivirals

Two classes of influenza antiviral dugs are licensed for treatment and prophylaxis, the M2 ion-channel blockers (M2Bs), amantadine (Symmetrel^{R}) and rimantadine (Flumadine^{R}, not registered in The Netherlands), and the neuraminidase inhibitors, oral oseltamivir (Tamiflu^{R}) and inhaled zanamivir (Relenza^{R}). M2Bs have been available since 1964, but their usefulness have been limited because of adverse effects, rapid development of resistance (full cross-resistance for both drugs) and lack of activity against influenza B virus infections. M2Bs are also indicated for Parkinson disease, confounding analysis of prescription data of M2Bs for influenza. An analysis of indications for prescribing amantadine in The Netherlands over the year 2007 revealed that prescriptions for which a diagnosis was reported (43% of total prescriptions) were mainly for chronic diseases like Parkinson disease (47%) and Multiple Sclerosis (20%), whilst influenza was not reported as diagnosis (Source: Landelijk Informatie Netwerk Huisartsenzorg; www.nivel.nl/linh). However, amantadine prescribed as prophylaxis might be included in the 57% of total prescriptions for which no diagnosis was reported. Nevertheless, amantadine prescriptions have a steady level in The Netherlands and show only minimal excess prescriptions during influenza seasons (Figure 1). The sudden increase in amantadine prescriptions in July 2008 is caused by a

Figure 1. Monthly prescription data for zanamivir, oseltamivir and amantadine for The Netherlands, 2003 – December 2008. Source: Stichting Farmaceutische Kengetallen, Den Haag, The Netherlands.



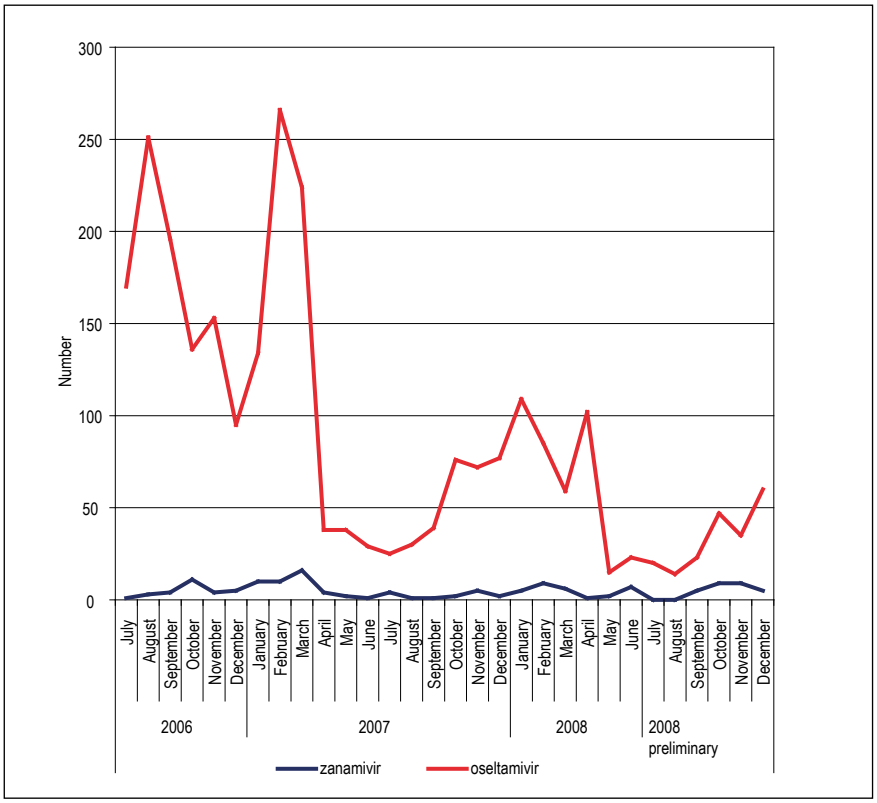
Download from SWAB.nl | 2026-11-12 14:20

change in billing of week dosing systems for medication of residents in nursing homes from biweekly to weekly (Source: Stichting Farmaceutische Kengetallen, Den Haag, The Netherlands). In fact, the quarterly number of Defined Daily Doses for amantadine shows a slight decreasing trend over the period 2003-2008.
The introduction of the neuraminidase inhibitors NAIs in 1999, that are active against both type A and B influenza viruses, was a major breakthrough in treatment and prophylaxis of influenza using antiviral drugs. In addition, because of different molecular interactions of both drugs with the neuraminidase a limited number of mutations result in full cross-resistance. According to prescription data, NAIs are not widely used in The Netherlands (Figures 1, 2). Highest prescription of 6,641 courses oseltamivir was noted in October 2005 (Figure 1), possibly due to personal stockpiling in response to the emergence of A (H5N1) in Turkey. In Europe the number of prescriptions by country is in general low, but The Netherlands is among the lowest (3). Prescriptions were highest in Japan since the 2001/2002 season and up to the 2006/2007 season (mean 77%, range 70% - 87%, of global prescriptions; n = 2 million to 11 million prescriptions per season globally), whilst in the 2007/2008 season prescriptions were highest in the USA (67% of global prescriptions; n = 6 million prescriptions) (Source: Intercontinental Marketing Services Health).

Surveillance for resistance

Until the introduction of the NAI in 1999 there was no systematic surveillance for resistance of influenza viruses to antiviral drugs, mostly because the M2Bs were only sporadically used in very specific situations. With the introduction of the NAIs the global network of WHO linked laboratories called Neuraminidase Inhibitor Susceptibility Network (NISN; www.nisn.org) was established with funding of pharmaceutical companies to monitor the development of resistance to these new drugs using virus isolates sent to the four WHO Collaborating Centres for Reference and Research on Influenza for vaccine recommendation purposes. In Europe, the Community Network of Reference Laboratories for Human Influenza operating since 2003 within the EU funded European Influenza Surveillance Scheme started in 2004 in collaboration with the EU funded project European surveillance network for vigilance against viral resistance (VIRGIL) monitoring of antiviral resistance to M2Bs and NAIs and implementation of national capacity for antiviral susceptibility monitoring as part of pandemic preparedness plans and the demand for guidance for antiviral therapy and prophylaxis on a patient level and during outbreaks (4-6). Since September 2008, this European monitoring of antiviral susceptibility is carried out under the aegis of the European Centre for Disease Prevention and Control (ECDC) in Stockholm,

Figure 2. Monthly prescription data for zanamivir and oseltamivir for The Netherlands, July 2006 – December 2008. Source: Stichting Farmaceutische Kengetallen, Den Haag, The Netherlands.



Download from SWAB.nl | 2026-11-12 14:20

Sweden. In The Netherlands, monitoring of antiviral susceptibility is since the 2005/2006 season embedded in the integrated clinical and virological surveillance of influenza using general practitioner (GP) sentinel stations, which is carried out by the NIVEL Netherlands institute for health services research and the National Influenza Centre location Bilthoven, Centre for Infectious Disease Control, National Institute for Public Health and the Environment.

Techniques used to monitor antiviral resistance in influenza viruses are determination of the 50 percent inhibitory concentration (IC50) in cell-ELISA virus growth inhibition assay or plaque reduction assay and Sanger sequencing, pyrosequencing or site-specific polymerase chain reaction (PCR) assay for known resistance markers for both the M2Bs and NAIs (7, 8). For NAIs, the IC50 can also be determined using an enzyme inhibition assay (9, 10).

Resistance

Although development of resistance to M2Bs under therapy is rapid, influenza viruses naturally resistant to M2Bs were not detected globally until 2002. Since the 2002/2003 season A(H3N2) influenza viruses naturally resistant to M2Bs by S31N mutation in the M protein rapidly expanded globally to levels near 100% from the 2005/2006 season onward (11-13). Also in The Netherlands, since the start of M2B resistance monitoring during the 2005/2006 season, the proportion resistant viruses increased from about 75% during the 2005/2006 and 2006/2007 seasons to 100% during the 2007/2008 and 2008/2009 seasons (Table 1). A similar phenomenon was observed in the A(H1N1) viruses in the period 2004/2005 – 2006/2007, however resistant clade 2A and 2C viruses were gradually replaced by susceptible clade 2B viruses since the 2006/2007 season (12, 13). In The Netherlands, A(H1N1) viruses detected during the 2006/2007 and 2007/2008 seasons were susceptible to M2Bs (Table 1).

Prior to the introduction of NAIs in 1999, and up to 2007, less than one percent of viruses tested from unselected surveillance studies in a number of countries worldwide demonstrated natural resistance to NAIs (14-18). Limited development of resistance to oseltamivir has been observed in treated individuals, with little evidence of onward transmission of resistant viruses, although low level transmission of resistant variants cannot be discounted. However, oseltamivir resistant viruses emerged in up to 18% (9/50) of treated Japanese children with A(H3N2) infection and 16% (7/43) of treated Japanese children with A(H1N1) infection, also with no evidence that these viruses transmitted efficiently (19, 20). In general, resistance mutations in the neuraminidase protein affect transmissibility and virulence of the influenza viruses and therefore resistant viruses emerging during therapy usually do not transmit (21, 22). In season 2007/2008, however, transmissible A(H1N1) influenza viruses resistant to oseltamivir due to H275Y mutation in the neuraminidase protein causing similar disease as susceptible A(H1N1) viruses emerged and were first detected in Europe (23, 24). These viruses are still susceptible to zanamivir and the M2Bs. During the season the proportion resistant A(H1N1) viruses increased to about 56% in Europe. Subsequently, these viruses emerged also during the Southern hemisphere 2008 season (25). Preliminary analysis of A(H1N1) viruses detected during the 2008/2009 Northern hemisphere season indicate near 100% resistant viruses (26). In The Netherlands also an increasing proportion oseltamivir resistant A(H1N1) viruses was observed during the 2007/2008 season, whilst the overall proportion resistant A(H1N1) viruses was 27%. Because of the importance of this phenomenon, the analysis of A(H1N1) viruses detected using sentinel specimen was extended with A(H1N1) viruses sent to the NIC location Erasmus Medical Centre, Rotterdam, originating from patients consulting GPs other than the sentinel GPs and hospitalized patients. The 2008/2009 season in

Table 1. Resistance of influenza viruses to neuraminidase inhibitors and M2 ion channel blockers in The Netherlands, 2005/2009 – 2008/2009[1]

Season	A(H3N2)	A(H1N1)	B		
	NAI	M2B	NAI	M2B	NAI
2005/2006	1/39 (3%)[2]	29/39 (74%)	NA	NA	2/48 (4%)[3]
2006/2007	0/50	38/51 (75%)	0/5	0/6	0/3
2007/2008	0/10	12/12 (100%)	47/172 (27%)[4]	0/49	1/81 (1%)[2]
2008/2009[5]	0/40	8/8 (100%)	5/5 (100%)	ND	ND

1 Results derived from virus isolates and directly from clinical specimens combined. Abbreviations: NAI = neuraminidase inhibitors; M2B = M2 ion-channel blockers; NA = not applicable as there were no viruses of the given type or subtype; ND = viruses available, but analysis was not been completed at the date of writing this report.

2 The resistant virus had an extreme outlier IC50 for oseltamivir and mild outlier IC50 for zanamivir.

3 Both resistant viruses had outlier IC50 values for oseltamivir as well as zanamivir.

4 Viruses resistant to oseltamivir only. Viruses were sensitive to zanamivir and M2Bs.

5 Preliminary data; analysis of the viruses from the 2008/2009 season is ongoing.

Download from SWAB.nl | 2026-11-12 14:20

The Netherlands was dominated by A(H3N2) influenza viruses, of which those analysed were resistant for M2Bs, whereas the few A(H1N1) viruses detected and analysed for NAI resistance were all resistant to oseltamivir (Table 1). Since the start of antiviral susceptibility monitoring in The Netherlands only sporadically A(H3N2) and B influenza viruses resistant to NAIs were detected. An overview of NAI susceptibility results in The Netherlands since the 2005/2006 season is shown in Table 1.

Impact resistance

Transmissible resistant influenza viruses seem not to differ in their clinical impact compared to sensitive viruses in normally healthy persons (27-29). However, resistance can particularly cause problems in the treatment of influenza in immunocompromised patients as shown in recent Dutch studies. Two immunocompromised patients with infections initially due to sensitive A(H1N1) virus that had emergence of resistance (H275Y) during oseltamivir therapy, one of whom had prolonged viral excretion and one of whom died of complications (30, 31). In another patient on chemotherapy for chronic lymphocytic leukemia and in respiratory failure due to infection with a resistant A(H1N1) virus, empiric oseltamivir therapy for 7 days was not associated with reductions in viral loads or improvements in clinical course (30, 32). Viral clearance was temporally associated with marrow recovery and perhaps therapy with amantadine and inhaled zanamivir, but this patient eventually died. A fourth patient with non-Hodgkin lymphoma infected with resistant A(H1N1) virus experienced upper respiratory infection with prolonged viral excretion, however, survived highly likely due to lymphocyte reconstitution (31). A nosocomial outbreak of oseltamivir-resistant influenza A(H1N1) virus involved four patients of which three immunocompromised (33). Two of the three immunocompromised patients died with influenza pneumonia, whilst the third immunocompromised patient survived showing viral clearance following lymphocyte reconstitution.

In addition, emergence of resistance to M2Bs and NAIs has important implications for pandemic preparedness activities, i.e. on policies which antiviral drugs to stockpile and on the validity of models for spread of antiviral resistant strains during the first phases of a pandemic (34, 35).

Conclusion

Emergence of resistance to M2Bs and NAIs in circulating A(H3N2) and A(H1N1) seasonal influenza viruses has resulted in considerable limitations in possibilities to treat severe influenza cases and for (post exposure) prophylaxis. Current strategies for application of influenza antivirals should include surveillance for antiviral resistance, immediate determination of antiviral susceptibility when treatment of severe cases of influenza is considered and monitoring treatment by viral load and antiviral susceptibility measurements (36).

Acknowledgements

The authors thank Gé Donkers, coordinator of the GP sentinel network at NIVEL, Utrecht, and the GPs and their patients for providing clinical specimens, and Guus Rimmelzwaan and Ruud van Beek from Erasmus MC, Rotterdam, for providing susceptibility data of A(H1N1) viruses sent to the Erasmus MC for antigenic characterisation by peripheral and hospital laboratories.

References

1. Cools HJM, Herngreen JJ, de Jong RE, Lichtenbelt MF, Rothbarth PH, van Essen GA. NVVA Richtlijn Influenzapreventie in verpleeghuizen en verzorgingshuizen, april 2004. ISBN nr. 90 807332 3 7.
2. Van Essen GA, Bueving HJ, Voordouw ACG, Berg HF, Van der Laan JR, Van Lidth de Jeude CP, Boomsma LJ, Opstelten W. NHG-Standaard Influenza en influenzavaccinatie. Eerste herziening. Huisarts en Wetenschap. 2008; 51: 1-12.
3. Kramarz P, Monnet D, Nicoll A, Yilmaz C, Ciancio B. Use of oseltamivir in 12 European countries between 2002 and 2007 – lack of association with the appearance of oseltamivir-resistant influenza A(H1N1) viruses . Euro Surveill 2009; 14(5): pii=19112.
4. Meijer A, Brown C, Hungnes O, Schweiger B, Valette M, van der Werf S, Zambon M; Virology Task Groups of the European Influenza Surveillance Scheme. Programme of the Community Network of Reference Laboratories for Human Influenza to improve Influenza Surveillance in Europe. Vaccine 2006; 24: 6717-23.
5. Meijer A, Lackenby A, Hay A, Zambon M. Influenza antiviral susceptibility monitoring activities in relation to national antiviral stockpiles in Europe during the winter 2006/2007 season. Euro Surveill 2007; 12 (4): E3-4.
6. Meijer A, Lackenby A, Taylor P, Lina B, van der Werf S, Enouf V, Pérez-Breña P, Pregliasco F, Rebelo de Andrade H, Wiman Å, Hay A, Paget J, Zambon M. Informatics assisting influenza antiviral susceptibility monitoring in Europe. In: Abstracts of the VIRGIL international symposium 2008 on antiviral drug resistance; Lyon, France; 2008 May 26-27; Abstract 1.
7. Tisdale M. Monitoring of viral susceptibility: new challenges with the development of influenza NA inhibitors. Rev Med Virol 2000; 10: 45-55.
8. Lackenby A, Democratis J, Siqueira MM, Zambon MC. Rapid quantitation of neuraminidase inhibitor drug resistance in influenza virus quasispecies. Antivir Ther 2008; 13: 809-20.
9. Potier M, Mameli L, Bélisle M, Dallaire L, Melançon SB. Fluorometric assay of neuraminidase with a sodium (4-methylumbelliferyl-alpha-D-N-acetylneuraminate) substrate. Anal Biochem 1979; 94: 287-96.
10. Buxton RC, Edwards B, Juo RR, Voyta JC, Tisdale M, Bethell RC. Development of a sensitive chemiluminescent neuraminidase assay for the determination of influenza virus susceptibility to zanamivir. Anal Biochem 2000; 280: 291-300.
11. Bright RA, Medina MJ, Xu X, Perez-Oronoz G, Wallis TR, Davis

Download from SWAB.nl | 2026-11-12 14:20

XM, Povinelli L, Cox NJ, Klimov AI. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet 2005; 366: 1175-81.
12. Deyde VM, Xu X, Bright RA, Shaw M, Smith CB, Zhang Y, Shu Y, Gubareva LV, Cox NJ, Klimov AI. Surveillance of resistance to adamantanes among influenza A(H3N2) and A(H1N1) viruses isolated worldwide. J Infect Dis 2007; 196: 249-57.
13. Saito R, Suzuki Y, Li D, Zaraket H, Sato I, Masaki H, Kawashima T, Hibi S, Sano Y, Shobugawa Y, Oguma T, Suzuki H. Increased incidence of adamantane-resistant influenza A(H1N1) and A(H3N2) viruses during the 2006-2007 influenza season in Japan. J Infect Dis 2008; 197: 630-2; author reply 632-3.
14. Neuraminidase Inhibitor Susceptibility Network. Use of influenza antivirals during 2003-2004 and monitoring of neuraminidase inhibitor resistance. Wkly Epidemiol Rec 2005; 80: 156.
15. McKimm-Breschkin J, Trivedi T, Hampson A, Hay A, Klimov A, Tashiro M, Hayden F, Zambon M. Neuraminidase sequence analysis and susceptibilities of influenza virus clinical isolates to zanamivir and oseltamivir. Antimicrob Agents Chemother 2003; 47: 2264-72.
16. Monto AS, McKimm-Breschkin JL, Macken C, Hampson AW, Hay A, Klimov A, Tashiro M, Webster RG, Aymard M, Hayden FG, Zambon M. Detection of influenza viruses resistant to neuraminidase inhibitors in global surveillance during the first 3 years of their use. Antimicrob Agents Chemother 2006; 50: 2395-402.
17. Hurt AC, Barr IG. Influenza viruses with reduced sensitivity to the neuraminidase inhibitor drugs in untreated young children. Commun Dis Intell 2008; 32: 57-62.
18. Sheu TG, Deyde VM, Okomo-Adhiambo M, Garten RJ, Xu X, Bright RA, Butler EN, Wallis TR, Klimov AI, Gubareva LV. Surveillance for neuraminidase inhibitor resistance among human influenza A and B viruses circulating worldwide from 2004 to 2008. Antimicrob Agents Chemother 2008; 52: 3284-92.
19. Kiso M, Mitamura K, Sakai-Tagawa Y, Shiraishi K, Kawakami C, Kimura K, Hayden FG, Sugaya N, Kawaoka Y. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. Lancet 2004; 364: 759-65.
20. Ward P, Small I, Smith J, Suter P, Dutkowski R. Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. J Antimicrob Chemother 2005; 55 Suppl 1:i5-i21.
21. Ives JA, Carr JA, Mendel DB, Tai CY, Lambkin R, Kelly L, Oxford JS, Hayden FG, Roberts NA. The H274Y mutation in the influenza A/H1N1 neuraminidase active site following oseltamivir phosphate treatment leave virus severely compromised both in vitro and in vivo. Antiviral Res 2002; 55: 307-17.
22. Herlocher ML, Truscon R, Elias S, Yen HL, Roberts NA, Ohmit SE, Monto AS. Influenza viruses resistant to the antiviral drug oseltamivir: transmission studies in ferrets. J Infect Dis 2004; 190: 1627-30.
23. Lackenby A, Hungnes O, Dudman SG, Meijer A, Paget WJ, Hay AJ, Zambon MC. Emergence of resistance to oseltamivir among influenza A(H1N1) viruses in Europe. Euro Surveill 2008; 13(5) pii: 8026.
24. Meijer A, Lackenby A, Hungnes O, Lina B, van-der-Werf S, Schweiger B, Opp M, Paget J, van-de-Kassteele J, Hay A, Zambon M; European Influenza Surveillance Scheme. Oseltamivir-resistant influenza virus A (H1N1), Europe, 2007-08 Season. Emerg Infect Dis 2009; 15: 552-60.
25. Besselaar TG, Naidoo D, Buys A, Gregory V, McAnerney J, Manamela JM, Blumberg L, Schoub BD. Widespread oseltamivir resistance in influenza A viruses (H1N1), South Africa. Emerg Infect Dis 2008; 14: 1809-10.
26. Goddard N, Zucs P, Ciancio B, Plata F, Hungnes O, Mazick A, Meijer A, Hay A, Daniels R, Nicoll A, Zambon M. Start of the influenza season 2008-9 in Europe - increasing influenza activity moving from West to East dominated by A(H3N2). Euro Surveill 2009; 14(3) pii: 19097.
27. Meijer A, Dijkstra F, Donker GA, van Beek R, Jonges M, van der Sande MAB, et al. Emergence of oseltamivir resistant influenza A(H1N1) viruses in The Netherlands during the winter 2007/2008. Programme and Abstract Book for the Third European Influenza Conference, Portugal, September 14-17, 2008; 169 (abstr 6-021). 2008.
28. Hauge SH, Dudman S, Borgen K, Lackenby A, Hungnes O. Oseltamivir-resistant influenza viruses A (H1N1), Norway, 2007-08. Emerg Infect Dis 2009; 15: 155-62.
29. Dharan NJ, Gubareva LV, Meyer JJ, Okomo-Adhiambo M, McClinton RC, Marshall SA, St George K, Epperson S, Brammer L, Klimov AI, Bresee JS, Fry AM; Oseltamivir-Resistance Working Group. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. JAMA 2009; 301: 1034-41.
30. van der Vries E, Wensing AMJ, Schutten M, Meijer A, van den Berg B, de Lange DW, van Doornum GJJ, Osterhaus ADME, Boucher CAB. Two fatal oseltamivir resistant influenza A(H1N1) infections in immunocompromised patients during the 2007/2008 influenza season in The Netherlands. The Third European Influenza Conference, Vilamoura, Portugal, 14-17 September 2008, Addendum & Participants List, 21-22 (Abstract 6-034). 2008.
31. Gooskens J, Jonges M, Claas EC, Meijer A, Kroes AC. Prolonged excretion of influenza virus and frequent development of antiviral resistance. The Third European Influenza Conference, Vilamoura, Portugal, 14-17 September 2008, Addendum & Participants List, 19 (Abstract 6-028). 2008.
32. Van der Vries E, van den Berg B, Schutten M. Fatal oseltamivir-resistant influenza virus infection. The New Engl J Med 2008; 359: 1074-6.
33. Gooskens J, Jonges M, Claas EC, Meijer A, van den Broek PJ, Kroes AM. Morbidity and mortality associated with nosocomial transmission of oseltamivir-resistant influenza A(H1N1) virus. JAMA 2009; 301:1042-6.
34. Lackenby A, Thompson CI, Democratis J. The potential impact of neuraminidase inhibitor resistant influenza. Curr Opin Infect Dis 2008; 21:626-38.
35. Fleming DM, Elliot AJ, Meijer A, Paget WJ. Influenza virus resistance to oseltamivir: what are the implications? Eur J Public Health 2009 Feb 12. [Epub ahead of print]
36. Jonges M, van der Vries E, Meijer A, Boucher CAB. Waakzaamheid bij profylaxe en therapie van influenzavirus infecties in het licht van gedetecteerde oseltamivir resistente A(H1N1) virussen in het 2007-2008 griepseizoen. Ned Tijdschr Med Microbiol 2008;16: 20-24.

Download from SWAB.nl | 2026-11-12 14:20

Appendix

List of abbreviations

ATC	Anatomical Therapeutic Chemical classification system
ATCC	American Type Culture Collection
CBO	Institute for Quality in Healthcare
CBS	Statistics Netherlands, i.e. the Central Statistical Office of the Netherlands
CFU	Colony Forming Units
CIDC	Central Institute for Animal Disease Control
CLSI	Clinical and Laboratory Standards Institute (formerly NCCLS)
COPD	Chronic Obstructive Pulmonary Disease
CRG	Dutch Committee on Guidelines for Susceptibility Testing
DDD	Defined Daily Dose
CVZ	College for Health Care Insurance's
EARSS	European Antimicrobial Resistance Surveillance System
ECCMID	European Congress on Clinical Microbiology and Infectious Diseases
ESAC	European Surveillance of Antibiotic Consumption
ESBL	Extended Spectrum Beta-lactamase
EU	European Union
GIP	Drug Information Project
GP	General practitioner
GRAS	Gonococcal Resistance to Antimicrobials Surveillance
IPCI	Integrated Primary Care Information
ISIS	Infectious Diseases Information System
LINH	Netherlands Information Network in General Practice
MIC	Minimal Inhibitory Concentration
MRSA	Methicillin Resistant Staphylococcus aureus
MSSA	Methicillin Sensitive Staphylococcus aureus
NCCLS	National Committee for Clinical Laboratory Standards
NHG	Dutch College of General Practitioners
NIVEL	Netherlands Institute of Health Services Research
NVMM	Netherlands Society for Medical Microbiology
PRISMANT	Institute for Health Care Information and Consultancy
RIVM	National Institute of Public Health and the Environment
SERIN	Surveillance of Extramural Resistance in the Netherlands
SFK	Foundation for Pharmaceutical Statistics
SIRIN	Surveillance of Intramural Resistance in the Netherlands
STI	Sexually Transmitted Infection
SWAB	Foundation of the Dutch Working Party on Antibiotic Policy
WIP	Working Party on Infection Prevention
WHO	World Health Organisation

Download from SWAB.nl | 2026-11-12 14:20

Demographics and numerator data

Table A Trend in the number of inhabitants in the Netherlands (Source: CBS)

Year	Number of inhabitants (1 January)
1997	15 567 107
1998	15 654 192
1999	15 760 225
2000	15 863 950
2001	15 987 075
2002	16 105 285
2003	16 192 572
2004	16 258 032
2005	16 305 526
2006	16 334 210
2007	16 357 992
2008	16 407 619

Table B Resource indicators of acute Hospital care in the Netherlands (Source: CBS)

Year	Hospitals	Discharges (x 1000)	Bed-days (x 1000)	Length of stay (mean in days)
1998	115	1524	13800	9.1
1999	109	1501	12985	8.7
2000	104	1460	12386	8.5
2001	101	1458	11912	8.2
2002	98	1501	12086	8.1
2003	97	1574	11800	7.5
2004	97	1656	11759	7.1
2005	96	1681	11515	6.9
2006	96	1736	11447	6.6

Table C Resource indicators of University Hospital care in the Netherlands (Source: CBS)

Year	Hospitals	Discharges (x 1000)	Bed-days (x 1000)	Length of stay (mean in days)
1998	8	200	2032	10.2
1999	8	201	1914	9.5
2000	8	197	1842	9.4
2001	8	193	1805	9.4
2002	8	193	1820	9.4
2003	8	200	1837	9.2
2004	8	210	1830	8.7
2005	8	214	1825	8.5
2006	8	218	1806	8.3

Table D Resource indicators of General Hospital care in the Netherlands (Source: CBS)

Year	Hospitals	Discharges (x 1000)	Bed-days (x 1000)	Length of stay (mean in days)
1998	107	1324	11768	8.9
1999	101	1300	11071	8.5
2000	96	1263	10544	8.3
2001	93	1265	10107	8.0
2002	90	1308	10266	7.8
2003	89	1374	9963	7.3
2004	89	1446	9929	6.9
2005	88	1467	9690	6.6
2006	88	1518	9641	6.4

Download from SWAB.nl | 2026-11-12 14:20

Materials and methods

Surveillance of antibiotic use in humans

Data on the consumption of antibiotics were collected by a pre-established protocol, using the ATC/DDD classification that is developed by WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no). The Defined Daily Dose is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. It enables however comparison of drug consumption statistics at international and other levels. The 2008 update of the ATC/DDD classification system is used to calculate the number of DDDs in this report.

Primary health care

All antibiotics for human use are prescription-only medicines in the Netherlands. The majority of antibiotics are delivered to patients by community pharmacies. Direct delivery of medicines by general practitioners from their own pharmacy reaches approximately 8.4% of the Dutch population, mainly in rural areas (reference 1). Data on the use of antibiotics in primary health care were obtained from the Foundation for Pharmaceutical Statistics (SFK; http://www.sfk.nl) and expressed as the number of Defined Daily Doses (DDD) per 1000 inhabitants per day.

Sales data from approximately 90% of all community pharmacies (1615 out of 1800 community pharmacies) are transferred monthly to SFK in an electronically format. The data are subsequently weighted statistically and extrapolated to cover 100% of the deliveries by community pharmacies. The total number of DDDs is divided by the total number of inhabitants that is registered by a community pharmacy (approximately 91.6 of the total number of inhabitants in the Netherlands). Data on the number of inhabitants in the Netherlands are obtained from Statistics Netherlands (CBS; http://www.cbs.nl).

SFK data on antibiotic use do not include the use of antibiotics in hospitals. Antibiotics prescribed by hospital based medical specialists to their outpatients are however included. Deliveries from community pharmacies to nursing-homes as an institute are not covered.

Hospitals

Data on the use of antibiotics in Dutch hospitals were collected by the SWAB by means of a questionnaire distributed to all Dutch hospital pharmacists. The number of admissions and the number of days spent in the hospital (bed-days) are also registered in the questionnaire. The use of antibiotics is expressed as DDD/100 patient-days and in DDD/100 admissions (reference 2). The number of patient-days is calculated by subtracting the number of admissions from the number of bed-days to compensate for the fact that in the bed-days statistics both the day of admission and the day of discharge are counted as full days.

The total number of bed-days and discharged patients (approximates the number of admissions) were obtained from Statistics Netherlands (CBS; http://www.cbs.nl). Data from a sample of 60% of the hospitals are presented in this report.

References

1. Batenburg-Eddes T van, Berg Jeths A van den, Veen AA van der , Verheij RA, Neeling AJ de. Regional variations in use of pharmaceuticals. National Institute of Public health and the Environment. Bilthoven (The Netherlands), 2002. ISBN 90 6960 099 4.
http://www.rivm.nl/bibliotheek/rapporten/270556005.html
2. Filius PMG, Liem TBY, van der Linden PD, Janknegt R, Natsch S, Vulto AG and HA Verbrugh. An additional measure for quantifying antibiotic use in hospitals. J Antimicrob Chemother. 2005;55:805-808.

Download from SWAB.nl | 2026-11-12 14:20

Surveillance of antibiotic resistance and susceptibility testing

Community

Staphylococcus aureus

The prevalence of antibiotic resistance among *S. aureus* in the indigenous flora of nursing home residents without infections was determined.

Residents from six nursing homes in Maastricht (South of The Netherlands) and Utrecht (Central part of The Netherlands) were asked to give informed oral consent to take a nasal swab from the anterior nostrils. The swabs were sent to the microbiological laboratory of the University Hospital Maastricht. The swabs were analysed for the presence of *S. aureus* using standard microbiological methods which includes enrichment broth and the detection of catalase and coagulase enzymes. In addition, the susceptibility to the following antimicrobial agents was determined in micro-titre plates: penicillin, methicillin, erythromycin, tetracycline, clindamycin, cefaclor, rifampicin, ciprofloxacin, imipenem, meropenem, cefuroxime, linezolid and co-trimoxazole (MCS diagnostics, Swalmen, the Netherlands). The resistance to fusidic acid and mupirocin was determined by the disc-diffusion method. *Staphylococcus aureus* ATCC 29213 was used as reference strain. The breakpoints for resistance were according to the EUCAST guidelines.

The study was approved by the Ethical Committee of the University Hospital Maastricht.

The results were compared with the results of the study on the prevalence of antibiotic resistance among *S. aureus* in the indigenous flora of healthy volunteers. A total of 4000 individuals (age 18 – 75 years), taken from the municipal administration received an envelope by mail containing information about the study, instructions for taking a nasal swab from the anterior nostrils and material for returning the swab to the laboratory of Medical Microbiology in Maastricht. A total of 2369 swabs were received from this group.

Streptococcus pneumoniae

The carrier rate of *S. pneumoniae* in the indigenous flora of healthy persons was determined in three study groups: (1) healthy infants at the age of 0-4 years from 48 day care centres in the southern part of the Netherlands, (2) healthy young children at the age of 9 years living in the southern part of the Netherlands, and (3) healthy adults at the age of 60 and higher from three general practitioners (one in the northern and two in the southern part of the Netherlands). Nose swabs were taken from infants and throats swabs from young children and adults. The swabs from the young children were taken in close cooperation with public health officers of the Municipal Health Service GGD Zuid-Limburg (head Dr C Hoebe, staff members Dr P Jacobs and Mr R Boesten). The swabs were cultured by standard microbiological methods including use of a selective agar plate (Colistin Nalidixic acid). Strains were identified according to standard microbiological methods. The susceptibility was determined in micro-titre plates for the following antimicrobial agents: gentamicin, linezolid, ciprofloxacin, moxifloxacin, levofloxacin, clarithromycin, co-trimoxazole, trimethoprim, imipenem, vancomycin, teicoplanin, penicillin, amoxicillin, chloramphenicol, co-amoxiclav (ratio 4:1), meropenem, ceftazidime, cefaclor, cefuroxime, cefotaxime, clindamycin, rifampicin, tetracycline and cefixime (MCS diagnostics, Swalmen, the Netherlands).

Streptococcus. pneumoniae ATCC 49619 was used as the reference strain. The breakpoints for resistance were according to the EUCAST guidelines.

The study was approved by the Ethical Committee of the University Hospital Maastricht.

Neisseria gonorrhoeae

In 1999, the nationwide surveillance of antibiotic resistance of gonococci was discontinued and since then insight in gonococcal susceptibility patterns had been limited. Concern for increasing resistance to quinolones led to an annual RIVM survey of resistance of gonococci since 2002. Complete data on the number of diagnosis and results of antimicrobial susceptibility testing for 2002-2006 were provided by 24 of all 39 microbiological laboratories identified.

In 2006, a project called Gonococcal Resistance to Antimicrobials Surveillance (GRAS) has been implemented in the Netherlands. This surveillance project consists of systematically collecting data on gonorrhoea and standardised measurement of resistance patterns by using an E-test, linked with epidemiological data. Participants are STI clinics and associated laboratories that identify the majority of STI in high risk populations. Isolates are sent to RIVM for further analysis.

Neisseria meningitidis

From 1993-2008 the Netherlands Reference Laboratory for Bacterial Meningitis received isolates from CSF and/or blood of patients with meningococcal disease. These strains were submitted by 75 bacteriological laboratories distributed over the country. The susceptibility to penicillin was determined by the E-test method. Strains with MIC < 0.125 mg/l were recorded susceptible, with MIC 0.125-0.38 mg/l intermediate and with MIC >=0.5 mg/l resistant.

Mycobacterium tuberculosis

The first isolate of *M. tuberculosis* of each patient with tuberculosis in The Netherlands is routinely sent to the RIVM for susceptibility testing and confirmation of identification. Isolates obtained after more than six months from the same patient, are judged a new isolate.

Download from SWAB.nl | 2026-11-12 14:20

The susceptibility of the strains is tested quantitatively with a standard agar dilution assay according to the recommendations of the CLSI. The antibiotics chosen for reporting are INH, rifampicin, streptomycin and ethambutol. Resistance rates represent the proportion of moderately and fully resistant strains.
The susceptibility data of 10141 strains, isolated from 1998-2008 are presented in this report.

Hospitals

Isolates of major pathogenic species were derived from different sources of hospital departments.

Unselected Hospital Departments and Outpatient Clinics

The susceptibility data of strains isolated from clinical samples of patients from Unselected Hospital Departments (clinics and outpatient clinics) and general practice were routinely determined by regional public health laboratories and local microbiology laboratories and aggregated through the national Infectious Diseases Information System for Antibiotic Resistance (ISIS-AR), which is coordinated by the Centre for Infectious Disease Control Netherlands (CIb) at the National Institute for Public Health and the Environment (RIVM). From 1998 to 2007, 11 regional public health laboratories and four local laboratories participated in this program. In 2007, ISIS-AR was revised by need of better definition and origin of strains, the more frequent use of automated systems for susceptibility testing and a more uniform use of international susceptibility criteria. In 2008, ten laboratories had already implemented the new ISIS-AR system, which means number of strains collected in 2008 is less than that in the previous years. On the other hand, the new system allowed us, e.g., to separate data collected from specific departments, outpatient clinics and general practice. Only the first isolate of each species from a patient was used for the study. The species distribution of isolates from various body sites appeared fairly stable during the period. Most isolates came from urine, respiratory tract, pus, wound and blood. The numbers of isolates per species and in each of these clinical materials in 2008 are given in table 1.
The susceptibility of the strains from the Unselected Hospital Departments was routinely and qualitatively or semi-quantitatively determined according to the standard techniques used in the individual laboratories. These methods included standardised agar diffusion assays as well as home-made or commercial broth micro-dilution assays. The breakpoints defined by the local laboratory were used for calculating resistance rates (R = resistant) for *E. coli*, *P. mirabilis*, *K. pneumoniae, E cloacae, P. aeruginosa, S. aureus* and *S. epidermidis*. Resistance rates for *H. influenzae, M. catarrhalis* and *S. pneumoniae* included strains that showed intermediate susceptibility (MIC > breakpoint for susceptibility).
The results over the years are presented as trends; we realized that it was not entirely correct to extend the trend line from 2007 to 2008, given the different number of participating centres and number of strains. However, studying the results, we observed no significant changes in trends in 2008 and therefore the trends were not discontinued in the figures. Further, in 2008 we excluded isolates from Intensive Care Units in our evaluation to avoid an unwanted mixture, because these were studied separately (see below). Strains from Outpatient Clinics and General Practice were separated and their data were compared with the data from the clinical departments. Both EUCAST and CLSI breakpoints were used and compared in the evaluation and differences were indicated when present.

Specific Hospital Wards

Unique unrelated consecutive isolates isolated from various clinical materials of patients admitted to Intensive Care Units, from urine of patients admitted to Urology Services and from respiratory specimens of patients admitted to Pulmonology Services were yearly collected from 1 March to 1 October. A maximum of 100 isolates per ward were collected each year. The strains were identified at the local laboratory for medical microbiology, stored at -20°C and then sent to a single laboratory (department of Medical Microbiology of the UMC St Radboud, Nijmegen between 1995 and 2001, and the department of Medical Microbiology of the University Hospital Maastricht from 2002 onwards) for quantitative susceptibility testing. A total of 28,500 strains were collected from 1996-2007, the results of 19,213 indicator strains (table 2) are presented in this report.
The susceptibility of the strains from the specific wards was determined quantitatively, i.e., by MIC determinations by broth micro-dilution assays using the recommendations of CLSI for *E. coli*, *P. mirabilis*, *K. pneumoniae*, *E. aerogenes*, *P. aeruginosa*, *E. faecalis*, *S. aureus* and *S. epidermidis*. Resistance rates of these organisms likewise represent the proportion of fully resistant strains. For *H. influenzae*, *M. catarrhalis* and *S. pneumoniae* both the lower breakpoints (MIC > breakpoint for susceptibility) and the breakpoint for resistance were used to enable comparison with the data of strains from Unselected Hospital Departments. *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247 and *S. aureus* ATCC 25923 were used as control strains in the MIC tests performed in the central laboratory.
Both EUCAST and CLSI breakpoints were used and compared in the evaluation and differences were indicated when present.

The antibiotics chosen for reporting were the antibiotics indicated by the Resistance Surveillance Standard of the SWAB published in 1999. This SWAB Resistance Surveillance Standard was also the guideline used for the

Download from SWAB.nl | 2026-11-12 14:20

Table 2. Number of indicator strains (N=19.213) isolated from patients admitted to specified hospital wards and tested for their susceptibility to antibiotics in the period 1998-2007.

Species	Intensive Care Units	Urology Services	Pulmonology Services
E. coli	2447	5164	
K. pneumoniae	527	649	
E. cloacae	371	155	
P. mirabilis	347	734	
P. aeruginosa	952	394	
E. faecalis	657	983	
S. aureus	903	302	
S. epidermidis	425	149	
S. pneumoniae			1346
H. influenzae			1823
M. catarrhalis			903

presentation of these data. The guideline provides criteria for indicator-organisms, indicator-antibiotics, methods and breakpoints to be used.

Facing page: Poster by M. Leverstein-van Hall, J. Muilwijk, E. Boel, J. Marcelis, R. Vreede, W. Dorigo-Zetsma, L. Sabbe, B. Hendrickx, J. Schellekens, and N. van de Sande-Bruinsma, entitled "First results of the new Dutch Infectious Diseases Surveillance Information System - Antimicrobial Resistance (ISIS-AR): Epidemiology of extended-spectrum beta-lactamases (ESBLs) in The Netherlands." presented at the 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Helsinki, Finland, 16-19 May, 2009.

Table 1. First isolates per clinical sample of patients in Unselected Hospital Departments in 2008.

Species (number of isolates)	Clinical material (number)			
	Blood N=3872	Pus and wound N=7680	Respiratory tract N=7673	Urine N=13,784
Gram-positive cocci				
Staphylococcus aureus (3986)	450	2129	1027	380
Coag neg. Staphylococcus (2123)	1192	556	17	358
Enterococcus spp. (3295)	233	901	114	2047
Streptococcus pneumoniae (1289)	347	66	875	1
Streptococcus agalactiae (663)	66	176	55	366
Streptococcus pyogenes (268)	65	161	26	16
Subtotal	2353	3989	2114	3168
Enterobacteriaceae				
Enterobacter cloacae (1165)	64	322	422	357
Escherichia coli (9651)	886	1536	832	6397
Klebsiella oxytoca (833)	65	193	238	337
Klebsiella pneumoniae (1854)	181	270	400	1003
Proteus mirabilis (1914)	72	356	215	1271
Other Enterobacteriaceae (1219)	81	262	477	399
Subtotal	1349	2939	2584	9764
Respiratory pathogens				
Haemophilus influenzae (1756)	25	62	1645	1
Neisseria meningitidis (35)	18	1	16	0
Subtotal	43	63	1661	1
Non-fermentors				
Acinetobacter baumannii complex (247)	10	63	118	56
Pseudomonas aeruginosa (2302)	106	564	867	765
Subtotal	116	627	985	821
Other				
Stenotrophomonas maltophilia (432)	11	62	329	30
Helicobacter pylori (66)				

Download from SWAB.nl | 2026-11-12 14:20

First results of the new Dutch Infectious Diseases Surveillance Information System-Antimicrobial Resistance (ISIS-AR).

Epidemiology of extended-spectrum beta-lactamases (ESBLs) in the Netherlands

M. Leverstein-van Hall, J. Muilwijk, E. Boel, J. Marcelis, R. Vreede, W. Dorigo-Zetsma, L. Sabbe, B. Hendrickx, J. Schellekens, N. van de Sande-Bruinsma (Bilthoven, Utrecht, Tilburg, Delft, Hilversum, Goes, Groningen, Terneuzen)

Background

In response to the widespread concerns about rising antimicrobial resistance in the Netherlands and the lack of consistent long-term surveillance covering all clinical relevant pathogens ISIS-AR was initiated mid 2007. ISIS-AR is a combined effort of the RIVM-Center for Infectious Disease Control, the Dutch Working Party on antibiotic policy and the Dutch Society for Medical Microbiology. It consists of a laboratory based surveillance system that collects monthly for each isolate the epidemiological and susceptibility data present in the laboratory information system of a clinical microbiological laboratory (CML). In 2008, the first 11 CMLs serving 28 hospitals were connected to ISIS-AR covering 34 pathogens. During 2008 the Guideline of the Dutch society for medical microbiology for screening and confirmation of extended-spectrum beta-lactamases (ESBLs) in *Enterobacteriaceae* was implemented.

Objectives

The aim of this study was to the determine the prevalence of *Escherichia coli* (EC) and *Klebsiella pneumoniae* (KP) isolates (intermediate) resistant (I/R) to 3d generation cephalosporins (CEPH3) in 1) blood and CSF isolates, and 2) urine isolates from the hospital (HOSP), out-patient-departments (OPD), long-term care facilities (LTCF) and general practitioner (GP). The extended-spectrum beta-lactamase (ESBL) prevalence and susceptibility patterns of these isolates test were further analyzed.

Methods

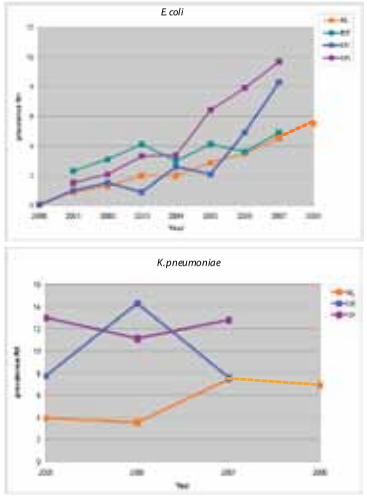
Data of the first isolate per species per body site per patient per patient-group per CML collected in 2008 were analyzed. Only clinical isolates were included.

Results

ESBL rates in Blood & CSF

The prevalence of isolates from blood & CSF I/R to CEPH3 was 5.2% and 7.9% (out of 814 EC and 164 KP resp). 80% of the blood and CSF isolates are nosocomial isolates. (*Fig 1*). Data of 2008 are ISIS-AR data, data before 2008 are EARSS data

Figure 1: Prevalence of *E. coli* and *K. pneumoniae* in blood & CSF isolates I/R to CEPH3

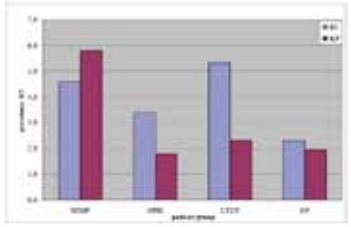


ESBL rates in urine isolates in- and outside the hospital

The prevalence of isolates from urine I/R to CEPH3 was 3.0% and 2.8% (out of 30.096 EC and 3.750 KP resp).

For EC the prevalences were 4.6% (216/4714) in the HOSP, 3.4% (223/6671) in the OPD, 5.3% (51/958) in LTCF and 2.3% (408/17807) in GP. For KP these were 5.8% (46/799), 1.8% (18/977), 2.3% (4/173) and 1.9% (35/1801) resp. (*Fig 2*).

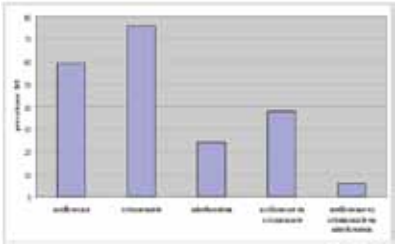
Figure 2: ESBLs are a problem in UTIs in- and outside the hospital.



ESBL & co-resistance in urine isolates from the general practitioner

ESBL positive EC (N=325) and KP (N=40) urine isolates from GP were R/I to norfloxacine in 59% (121/204), cotrimoxazole in 76% (160/211) and nitrofurantoin 24% (50/212). Co-resistance to the first 2 antibiotics existed in 38% (77/203) and to all 3 in 6% (13/203) *(Fig 3).*

Figure 3: Oral treatment for UTIs with ESBL positive isolates is endangered.



Type of ESBL as indicated by confirmation test

An ESBL confirmation test was performed in 65% (617/940) of the EC and 60% (70/116) of the KP (*Table 1*). The outcome of the confirmation test was more often negative or non-determinable in the urine isolates than in the blood isolates resp. 23% (152/651) and 13% (5/38).

Table 1: The outcome of the ESBL confirmation test.

		Total CEPH3 I/R N	tested	POS	NEG	NTB
			N(%)	N(%)	N(%)	N(%)
blood	ECO	42	31(69)	26(84)	3(10)	2(6)
	KPN	13	7(54)	7(100)	0	0
urine	ECO	898	588(65)	477(81)	130(22)	11(2)
	KPN	103	63(61)	52(82)	10(16)	1(2)

Conclusions

- **Dutch ESBL prevalence rates among blood and CSF isolates are increasing and have become similar to the rates in neighboring countries**
- **ESBLs have become a problem outside the hospital**
- **About half of the ESBL positive isolates is co-resistant to quinolones, aminoglycosides and cotrimoxazole**
- **Oral treatment of urinary tract infections with ESBL positive isolates is endangered**
- **Other resistance mechanisms than $ESBL_{TEM}$, $ESBL_{CTX-M}$ and $ESBL_{SHV}$ probably play a role in the decreased susceptibly to CEPH3 in urine isolates as well**

Download from SWAB.nl | 2026-11-12 14:20

Download from SWAB.nl | 2026-11-12 14:20